For discussion
on 18 July 2003

Legislative Council –
Panel on Security and Panel on Health Services
Joint Panel Meeting on 18 July 2003

Death of Inmate Mr CHEUNG Chi-kin in Siu Lam Psychiatric Centre on 19 November 2001

Purpose

This paper presents medical experts' opinions on the hypothesis raised by the Superintendent of Siu Lam Psychiatric Centre (SLPC) during the joint panel meeting on 5 March 2003 in relation to the death of an inmate in SLPC in November 2001, and sets out the Administration's response and proposed way forward in respect of the case.

Hypothesis

2. At the joint panel meeting of the Panel on Security and Panel on Health Services held on 5 March 2003 the Superintendent of SLPC, based on his own research into medical literature and the evidence adduced in the death inquest, put forward a hypothesis which might explain the high chlorpromazine level found in the blood of the deceased and some unusual needle marks found during autopsy. To recap briefly, the Superintendent hypothesised that the deceased, being a chronic diabetic patient, might have suffered from uncontrolled diabetes which could lead to cellular breakdown of adipose tissue (lipolysis) and the release of a large amount of chlorpromazine originally stored there.

Medical Experts' Opinions

3. We have invited three independent medical experts - Professor Karen S L LAM, Chair Professor in Medicine and Chief of Endocrinology of

the University of Hong Kong; Dr Bernard M Y CHEUNG, Associate Professor in Clinical Pharmacology, University of Hong Kong; and Professor Kenneth K C LEE, Professor and Head, Division of Pharmacy Practice, Chinese University of Hong Kong - to look into the hypothesis and to examine the medical issues which may be relevant to the death of the deceased. Their opinions are at **Annexes A, B and C** respectively.

4. The gist of the expert opinions is set out below –

Professor Karen S L LAM

- The deceased had a long history of diabetes mellitus (since childhood).

- The deceased did suffer from symptoms of severe hyperglycaemia (i.e. high blood glucose) and diabetic ketoacidosis (DKA) (an acute condition of uncontrolled diabetes requiring emergency treatment) during the few days prior to his death.

- Undiagnosed and untreated, those severe metabolic disturbances could lead to a fatal outcome.

- The deceased's post-mortem blood glucose level of 45.7 mmo1/L was higher than the mean level of 43.1 mmo1/L among 24 cases of death in diabetic coma reported by Gormsen et al (Forensic Sci Int 1985), all of whom had levels exceeding 19.44 mmo1/L, in contrast to low or undetectable post-mortem blood glucose levels in the controls who did not die of diabetic coma.

- Diabetic ketotic coma was a probable cause of death of the deceased.

- Markedly increased lipolysis or breakdown of fat occurring in DKA can theoretically lead to the release of drugs such as chlorpromazine previously cumulated in the fat issue. However, it is not possible to determine how and when such high tissue stores of chlorpromazine had built up in the deceased.

- The contribution of other probable causes, such as chlorpromazine toxicity cannot be excluded.

Dr. Bernard M Y CHEUNG

- Chlorpromazine is fat soluble.

- It is theoretically conceivable that lipolysis might have released a large amount of chlorpromazine and elevated the blood level of chlorpromazine in the blood, and might have contributed to the death of the deceased.

- Lipolysis and post-mortem redistribution could have markedly increased the level of chlorpromazine in the post-mortem blood.

- The three needle marks on the right shoulder and the associated bruises could be the result of attempted cannulation of the right cephalic vein. The three puncture sites overlie the course of the right cephalic vein. It is not the commonest site used for venous access, but can be used if more peripheral veins in the forearm or elbow are not accessible.

Professor Kenneth K C LEE

- The individual effects of chlorpromazine and methadone (as orally taken by the deceased according to the records during and immediately before his custody before death) should have had minimal contribution to the death of the deceased, as neither of the drugs had been taken in high enough doses to cause death.

- In order to cause a plasma chlorpromazine concentration of 9.7 μg/ml in the post-mortem blood, it is retrospectively calculated that, for example, some 1126 ampoules of the drug (50mg each) might need to be administered in a single dose 14 hours prior to the death, which was highly unlikely and physiologically impossible.

- The possibilities which caused the high plasma chlorpromazine concentration in the post-mortem blood could be –

  - Lipolysis as hypothesised, but this could only remain theoretical and the probability of occurrence should best be supported by experimental evidence.

  - A haemo-concentration effect arising from the loss of fluid due to uncontrolled diabetes leading to a shrink in blood volume.

- The occurrence of a post-mortem redistribution of drug from storage tissue where the concentration was high to areas of lower concentration e.g. blood.

- A combined effect of any of the above.

5. In view of the above, we have also invited Dr. MONG Hoi-keung[1], Consultant Forensic Pathologist in-charge of the Forensic Pathology Service of the Department of Health to review the original autopsy findings[2] and the original analysis of the body fluid samples of the deceased. His expert opinion is summarised as follows –

- With reference to the definition (and requirement) of the International Statistical Classification of Diseases by the World Health Organisation, it is in order to label the adverse effects of chlorpromazine, methadone and ethyl alcohol as Cause I (as the condition directly leading to death), and the condition of diabetes mellitus as Cause II (as a significant contributing cause to the death, but not related to Cause I), in the autopsy report. Any change to the present medical causes of death as depicted in the autopsy report is not required.

- As regards the high level of chlorpromazine in the blood, Dr MONG is prepared to accept the theoretical release due to lipolysis, other than an extrinsic source such as injection or ingestion.

- On the concentration of methadone, haemo-concentration due to dehydration as a result of DKA is noted. Dr MONG is prepared to accept that post-mortem production of ethyl alcohol might have been the sole reason for its presence found only in the blood (but not in the vitreous humour or urine).

- The needle marks found on the deceased were produced by big-gauge needles and were likely to be the result of failed attempts in inserting an intravenous line for infusion of fluid. The oozing of blood during autopsy is not inconsistent with failed resuscitation at Tuen Mun Hospital shortly before death (not more than an hour or two).

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[1] Dr MONG is on the Special Registry of the Hong Kong Medical Council in Forensic Pathology, and holds the professional qualifications of MBBS(HK), DMJ(CLIN)(LAS), DMJ(PATH)(LAS), FHKCPath and FHKAM(Pathology).

[2] The original autopsy showed that the cause of death was "Adverse effects of chlorpromazine, methadone and ethyl alcohol, with "Diabetes mellitus" listed under the category of "Other significant condition contributing to the death but not related to the disease or condition causing it".

The Administration's Observations and Response

6. As explained in paragraphs 15 to 18 of our previous Security Panel paper (CB(2)1323/02-03(01)), the deceased was subject to CCTV monitoring throughout his stay in the cell of SLPC and the local CCTV system had maintained about 17 hours of continuous, un-tampered videotape of activities in the cell leading up to the incident of discovery and rescue and shortly going beyond the incident. No irregularities have been detected from the examination of the videotape. The Police can confirm that of the 17 hours covered by the video footage, about 14 was the time immediately before the incident of discovery and rescue. Besides, according to the statements of the ambulancemen responsible, no needle marks at the shoulders of the deceased had been detected or recorded during the transfer of the deceased from SLPC to Tuen Mun Hospital for resuscitation and rescue. This fact was confirmed by one of the officers concerned under oath at the death inquest. (That said, the medical officer responsible for resuscitation of the deceased at Tuen Mun Hospital also stated in the death inquest that he had only undertaken intravenous injection at the left inner elbow. Thus, there is no concrete evidence to suggest who might have inflicted the needle marks on the deceased.)

7. All three medical experts who gave their opinion have accepted that it is theoretically possible that lipolysis had contributed to the high level of chlorpromazine in the blood of the deceased. While we have no information how and when such high tissue stores of chlorpromazine could have built up in the deceased, there is past medication record and anecdotal evidence during his previous custody in CSD institutions to suggest that he had had knowledge of, and possible dependence on, chlorpromazine for one reason or another. While staying in Hei Ling Chau Drug Addiction Treatment Centre (HLTC) in mid-December 1999, the deceased had been prescribed and administered with chlorpromazine continuously for 19 days. On one occasion on 15.12.1999, the prisoner received an ampoule of chlorpromazine (50mg/2ml) as prescribed to soothe his withdrawal syndrome. On 29.12.1999 the prisoner himself requested the Medical Officer of HLTC to increase the dose of chlorpromazine, claiming that the drug could cure his insomnia.

8. In view of all the above (paras. 4 – 7) and the medical experts' opinion, it appears that diabetic ketotic coma is a probable cause of death, although the degree of probability is difficult is establish retrospectively. Expert's opinion also considered that it was highly unlikely and physiologically impossible for the high concentration of chlorpromazine in the post-mortem blood to be caused by external injection.

9. We have carefully considered whether we should apply to the Court of First Instance for another death inquest into the incident pursuant to s.20(1) of the Coroners Ordinance[3], or to appoint a body to inquire into the incident pursuant to s.2(1) of the Commissions of Inquiry Ordinance[4]. We have decided against doing so on grounds of legal, medical and policy considerations, which include the following –

- Although there is arguably discovery of new evidence that may shed more light on the death of the deceased and although the hypothesis put forward is supported theoretically by expert evidence, conclusive evidence of the cause of the death and the actual occurrence of the lipolysis before death is still lacking.

- As things stand, the medical causes of death as recorded in the autopsy report appear to remain valid. The condition of diabetes mellitus was regarded as a significant contributing cause to the death in the autopsy report (cf. Dr. Mong's first point).

- Notwithstanding the new evidence, in any application for a new inquest, we need to satisfy the Court of First Instance that it is necessary or desirable that another inquest should be held. In this case, it is questionable if the new expert evidence might have made a material difference to the verdict recorded at the previous inquest, namely, that of "Open Verdict". If the verdict is likely to be the same, the Court would not be satisfied that a new inquest is necessary.

- The death of the deceased has already been the subject of investigation by the Police and a Death Inquest by the Coroner's Court. It has also been subject to deliberations in CSD's own Board of Inquiry and a special Task Group with two independent non-official Justices of the Peace as members to identify systemic

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[3] "(1) Where the Court of First Instance, upon the application in open court of a properly interested person or the Secretary for Justice, is satisfied -

(a) that a coroner has failed to hold an inquest which ought to be held;
(b) where an inquest has been held by a coroner, that by reason of fraud, rejection of evidence, irregularity of proceedings (including a failure to comply with section 14(3)), insufficiency of inquiry, or otherwise, it is necessary or desirable that another inquest should be held; or
(c) where an inquest has been held by a coroner, that by reason of the discovery of new facts or evidence it is necessary or desirable that another inquest should be held,

the Court of First Instance may order an inquest to be held into the death of a person and, where an inquest has been already held, may quash the findings of the coroner or jury at that inquest already held."

[4] "(1) The Chief Executive in Council may appoint one or more Commissioners (hereinafter referred to as a Commission) to inquire into the conduct or management of any public body, the conduct of any public officer or into any matter whatsoever which is, in his opinion, of public importance."

weaknesses and improvement measures required. Thorough discussions have been held at the Panel of Security and Panel of Health Services, and further detailed comments by independent medical experts have been obtained. Although worthy of thorough scrutiny, it appears that little is to be further gained from a new death inquest or inquiry into the incident that may better serve the public interest.

- As for the deceased's family, a new death inquest or inquiry may reopen wounds that may have started to heal, and unduly prolong their grief.

Way Forward

10. The Administration reaffirms its commitment to providing the best possible services to inmates for their safe custody and effective rehabilitation. The CSD will continue to implement the improvement measures it has identified and report the progress to the Security Panel as promised at the Panel meeting in January 2003. The CSD will also consider other practical options that could further improve the custodial and medical service arrangements for inmates.

Security Bureau
July 2003

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Expert Opinion

Re: Death Inquest CCDI-2139/2001 Prisoner CHEUNG Chi-kin

The deceased, aged 26 years at his time of death, has a long-standing history of diabetes mellitus since childhood. High levels of glucose and acetone were found in postmortem blood samples, suggesting that diabetic ketoacidosis, a serious acute complication of diabetes mellitus, had occurred antemortem and might have caused his death. To address this possibility adequately, it is important to have some basic understanding of his underlying medical condition.

I. What is diabetic ketoacidosis (DKA)?

Were the biochemical findings at postmortem in this case in keeping with severe DKA?

Diabetic ketoacidosis (DKA) refers to an acute condition of uncontrolled diabetes requiring emergency treatment with insulin and intravenous fluids. The cardinal biochemical features are hyperglycaemia (high blood glucose), hyperketonaemia (high blood ketones) and metabolic acidosis.

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DKA occurs when a diabetic patient with an absolute, or more commonly, a relative deficiency of insulin has an increased secretion of stress hormones (glucageon, catecholamines, cortisol and growth hormone), in response to an acute intercurrent illness.

In normal individuals and well-treated diabetic patients, there is sufficient insulin action to prevent the overproduction of glucose and ketone bodies by the liver. Insulin also promotes protein and fat synthesis and prevents their undue breakdown or catabolism.

Hyperglycaemia occurs in DKA because, without adequate insulin action, blood glucose cannot get into body cells to produce energy. Furthermore, uninhibited by insulin, the liver continues to produce glucose excessively, under the stimulation of the stress hormones.
The stress hormones, which promote catabolism of fat and protein, will also lead to excessive breakdown of fat (lipolysis) from the fat tissue, releasing large quantities of long-chain free fatty acids. These fatty acids are used by the liver to produce energy or produce ketone bodies, which include 3-hydroxybutyrate, acetoacetate and **acetone** which is formed from acetoacetate by spontaneous decarboxylation. Hence, without adequate insulin to suppress ketone formation, **hyperketonaemia** will ensue.

The ketones are strong organic acids that dissociate fully at physiological pH to equimolar amounts of hydrogen ions. In DKA, the rapid rise in the plasma hydrogen ion concentration outstrips the body's buffering capacity, leading to **metabolic acidosis** of increasing severity.

In a living person, the normal blood glucose level lies between 4 to 8 mmol/L. It has been found that blood glucose levels in postmortem blood samples tend to be considerably lower

in both diabetic and non-diabetic subjects relative to the antemortem status.

Gormsen & Lund (ref. 1) found that the mean blood glucose level was 43.1 mmol/L (776 mg/dl) in post-mortem peripheral venous samples of 24 cases of death in diabetic coma. All had levels exceeding 19.44 mmol/L (350 mg/dl). On the other hand, in a control group of deaths due to other causes the blood glucose was usually low and often zero, and all values were well below the low limit of the diabetic subjects. **They concluded that a blood glucose level above 19.44 mmol/L in the post-mortem sample obtained from a peripheral vein would indicate that death occurred in diabetic coma.**

In normal subjects and well-treated diabetic patients, blood acetone is usually undetectable unless there has been prolonged fasting. *With regard to acetone level in post-mortem blood samples, this was found to be a valuable indicator of antemortem hyperglycaemia in diabetic subjects in a study of 328 autopsy cases by Peclet et al (ref. 2). They also found that it was not affected by resuscitation.*

In this case, the findings of a blood glucose level of 45.7 mmol/L in the postmortem venous sample of the deceased would suggest that an even more severe degree of hyperglycaemia had been present before death. With reference to the findings and conclusions in reference 1, this high level of postmortem blood glucose would indicate death in diabetic coma.

At postmortem, the deceased was also found to have very high urine and blood acetone levels: urine acetone 45 mg /100ml (normal being undetectable) and blood acetone 6 mg

/100ml (normal 0.3-2 mg /100 ml). This degree of hyperketonaemia, taken together with the severe hyperglycaemia, would be confirmative of antemortem DKA, even though no biochemical assessment for metabolic acidosis had been performed.

II. **Was the past medical history of the deceased compatible with the hypothesis that DKA indeed occurred before death?**

Although DKA usually affects young patients with type 1 or insulin dependent diabetes mellitus, it can also occur in patients with type 2 or non-insulin dependent diabetes mellitus at times of intercurrent illness, when the impaired insulin secretion of the patient is further suppressed by the increased levels of stress hormones especially catecholamines.

According to the medical report from the Medical Clinic, Queen Elizabeth Hospital (QEH), dated 1/2/2002T, the deceased had diabetes mellitus since childhood. He was described as obese. According to the psychiatric medical record in 1998 during his admission to SLPC from 24/11/1998 to 8/12/1998, he was only treated with an oral drug metformin (500 mg tds), usually prescribed for obese type 2 diabetic patients. At his last follow-up at the QEH, he was also prescribed daonil, suggesting that his diabetes had become more severe so that a drug that stimulates insulin secretion has to be used as well. The QEH medical report also stated that he had poor compliance to diet control and drug treatment. Indeed, he had not returned to QEH for follow-up since 21/11/1999, 2 years prior to his death. The finding of gliclazide, another drug that stimulates insulin secretion, in the postmortem blood suggests that he had required drugs, obtained from other sources, to treat his diabetes. The absence of gliclazide in his urine, and the

fact that no anti-diabetic treatment had been given to him since 14/11/2001 when he was admitted to the LCKRC, suggest that the gliclazide of therapeutic level became detectable in the postmortem blood as a result of postmortem redistribution.

It is well known that good control of diabetes requires the co-operation of the patient himself. As noted in the QEH record, the deceased was uncooperative and gave inconsistent history during medical consultations so that appropriate or successful treatment could not be expected. It is highly likely, therefore, that his diabetes mellitus had been poorly controlled all along. Prolonged hyperglycaemia can itself accelerate the deterioration of the pancreatic cells that produce insulin. Indeed, at postmortem his pancreas showed a decrease in the number of islets of Langerhans (structure which secretes insulin), in keeping with long-standing diabetes with insulin deficiency.

He was addicted to heroin since 1993, changing from inhalation to injection in 1996, despite the fact that he first registered into the methadone treatment program in 1995. He had 7 drop-outs and 6 readmissions at the methadone program and had been continuing with his heroin injections with the last injection being allegedly taken two months prior to death. During the five days prior to death he had complained repeatedly of withdrawal symptoms despite the prescription of methadone. He allegedly took some shampoo on 16/11/2001 and complained of epigastric pain and vomiting of coffee ground material afterwards. The presence of multiple acute erosions were found in the stomach at postmortem, confirming the diagnosis of gastritis.

The information from the medical reports from QEH and SLPC, and the autopsy findings would suggest that in this patient with long-standing, poorly controlled type 2 diabetes,

significant insulin deficiency had developed. Furthermore, starting from five days prior to death he had suffered from significant withdrawal symptoms consequent to the longstanding opiate addiction. He also had pain and gastrointestinal bleeding caused by acute gastritis, induced by stress and/or shampoo ingestion. The opiate withdrawal syndrome and acute gastritis probably led to marked stress hormone responses, precipitating the development of DKA. The withholding of the oral anti-diabetic drugs could have attributed to the hyperglycaemia in this patient with pre-existing poorly controlled diabetes.

III. **Were there clinical evidence of DKA before death in this patient?**

In a patient with DKA, the high blood glucose exceeds the ability of the kidney to retain glucose, and glucose is lost in the urine together water and electrolytes. As a result, the patient passes a lot of urine, and thus becomes thirsty and dehydrated. Hyperventilation and vomiting further exacerbate the loss of water and electrolytes. In adults, the average loss of body water is approximately 5 litres.

Weight loss can be severe in the course of several days, largely attributed to the loss of water and breakdown of fat.

The severe water loss leads to **a rise in heart rate** and a fall in blood pressure. The loss of water and electrolytes, and protein breakdown also lead to **severe tiredness and generalized weakness.** Acidosis initially stimulates respiration as the body tries to reduce the acidosis by blowing out carbon dioxide. **Fast and deep breathing, or hyperventilation,** is thus a common clinical

feature of DKA. Gastrointestinal symptoms such as **abdominal pain** (consequent to the metabolic disturbance), **nausea and vomiting** are common.

The symptoms of DKA usually develop over several days. Untreated, **drowsiness ensues, leading eventually to coma and death.**

According to the medical records provided, the deceased weighed 84 kg on 14/11/2001 and 65 kg at autopsy on 22/11/2001. A reduction of 19 kg had occurred during the interval. Even allowing for postmortem changes, a drastic weight loss had occurred, in keeping with the diagnosis of DKA. Tired and weakness were on 17/11/2001 at the SLPC. Hyperventilation was obviously present on 17/11/2001, with the respiratory rate being recorded as 28/min, 24/min and 22/min on different occasions. The term "hyperventilation" was actually used in the medical record on 18/11/2001. He also had tachycardia with the pulse rate being 120/min, again recorded on several occasions on 17/11/2001: this was in striking contrast to the pulse rate of 75/min recorded on 16/11/2001, even when he was complaining of ***epigastric pain. Furthermore, he was reported to have a poor appetite especially on 18/11/2001. Vomiting and epigastric pain*** *since 16/11/2001 may have been caused by either gastritis or DKA.*

In summary, the deceased had many clinical features of DKA during the few days prior to death, especially on 17/11/2001 and 18/11/2001, including marked weight loss, tachycardia, hyperventilation, tiredness and weakness, anorexia and vomiting. Unfortunately, no blood sugar had been measured at the SLPC or QEH, despite the history of diabetes mellitus, so that the diagnosis was completely missed antemortem.

IV. Could DKA be responsible for his fatal outcome?

Acidosis has a negative effect on the contraction of heart muscles. It can lead to increased risk of ventricular arrhythmias. It can also lead to further fall in blood pressure through dilating the peripheral blood vessels. While acidosis has an initial stimulatory effect on respiration, **severe acidosis may lead to death through respiratory depression.**

In a person who is drowsy or comatose due to DKA or other causes including drug overdose, death due to aspiration of vomitus may occur. In this patient, the presence of coffee ground material in the mouth as noted on arrival at the A&E Department of Tuen Mun Hospital, the finding at autopsy of regurgitated stomach content in the oesophagus and heavily blood-stained fluid in the air passages down to the small airways would suggest that vomiting and, possibly, aspiration had occurred shortly before death.

Treatment of patients with such a severe degree of hyperglycaemia requires the use of insulin and intravenous fluid rehydration, even in the absence of ketoacidosis. In patients with very severe acidosis, sodium bicarbonate is also required. Even with insulin therapy, average mortality amounts to about 7%.

Before the introduction of insulin in 1923, DKA was invariably fatal (ref. 3).

In this patient, no insulin was given as the hyperglycaemia was completely missed before death, a fatal outcome was to be expected, although the contribution of other causes such as chlorpromazine toxicity can not be excluded.

V. Other issues

1. Could lipolysis lead to the high level of chlorpromazine in this patient?

As discussed under Section I, markedly increased lipolysis or breakdown of fat occurs in DKA and can theoretically lead to the release of fat-soluble drugs, such as chlorpromazine, previously cumulated in the fat tissue. On the other hand, postmortem redistribution from various organs and tissues may have led to further increase in the blood level of chlorpromazine in this case. As discussed in Section II, there was evidence of postmortem redistribution leading to the detection of therapeutic levels of gliclazide in the postmortem blood sample. However, it is not possible, from the information provided, to determine how and when such high tissue stores of chlorpromazine had build up in the deceased.

2. Could the reading of ethyl alcohol of 111 mg/100 ml in this case be a result of postmortem changes? Could postmortem changes or decomposition of the deceased also cause the oozing of blood from the needle mark during autopsy?

Postmortem tissue decomposition and putrefaction can lead to the formation of ethyl alcohol. In the autopsy report, patchy decomposition was found in the stomach. However, although the autopsy was performed 3 days after death, it was commented in the autopsy report that there was no evidence of putrefaction. The opinion of an expert in pathology should be sought if these are important issues

VI. Conclusion

Based on the past medical history, clinical features recorded during the five days prior to death and the autopsy findings, we can conclude that the deceased did suffer from severe hyperglycaemia and diabetic ketoacidosis during the few days prior to his death. Undiagnosed and untreated, these severe metabolic disturbances could lead to a fatal outcome. Diabetic ketotic coma was thus a probable cause of death in this case. However, the contribution of other probable causes, such as chlorpromazine toxicity, to his death cannot be excluded.

References

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May 6, 2003.

The diagnostic value of postmortem blood glucose determinations in cases of diabetes mellitus.

Gormsen H - *Forensic Sci Int* - 1985 Jun-Jul; 28(2): 103-7
From NIH/NLM MEDLINE

Ref 1

NLM Citation ID:
4043894 (PubMed}
86006532 (MEDLINE)

Full Source Title:
Forensic Science International

Publication Type:
Journal Article

Language:
English

43.11 mmol/L (mM)
776 mg/dL

350 mg/dl

19.4 mM

Authors:
Gormsen H; Lund A

Abstract:
In 24 cases of death in diabetic coma the peripheral venous blood showed glucose levels exceeding 3.5 mg/ml (mean value 7.76 mg/ml). In a control material of deaths of other causes the blood glucose was usually low and often zero, and all values were well below the lower limit of the diabetic concentrations. The acetone contents of the diabetic blood varied widely and were of limited diagnostic value. We conclude that glucose concentrations above 3.5 mg/ml in the peripheral blood indicate that death occurred in diabetic coma.

Major Subjects:

- Blood Glucose / * analysis
- Diabetic Coma / * blood / diagnosis
- Postmortem Changes

Additional Subjects:

- Human
- Ketone Bodies / blood / urine

Chemical Compound Name:
(Blood Glucose); (Ketone Bodies)

The use of vitreous humor levels of glucose, lactic acid and blood levels of acetone to establish antemortem hyperglycemia in diabetics.

Péclet C - *Forensic Sci Int* - 01-Mar-1994; 65(1): 1-6
From NIH/NLM MEDLINE

Ref 2

NLM Citation ID:
8206449 (PubMed}
94266232 (MEDLINE)

Full Source Title:
Forensic Science International

Publication Type:
Journal Article

Language:
English

Author Affiliation:
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Authors:
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Abstract:
Glucose and lactic acid concentrations were measured in 328 autopsy cases. Glucose and lactic acid in vitreous humor and blood levels of acetone were found to be valuable indicators of antemortem hyperglycemia in diabetics. Resuscitation significantly increased glucose concentrations in vitreous humor whereas blood levels of acetone were not significant (< 1 mg/dl: detection limit). Values encountered in postmortem cases are presented and case results are discussed.

Major Subjects:

- Acetone / * blood
- Death, Sudden / * etiology
- Diabetes Mellitus / * metabolism
- Glucose / * analysis
- Hyperglycemia / * diagnosis
- Lactates / * analysis
- Vitreous Body / * chemistry

Additional Subjects:

- Adolescence
- Adult
- Aged
- Aged, 80 and over
- Autopsy
- Child
- Child, Preschool
- Human

Ref 3

49 Diabetic Ketoacidosis, Non-Ketotic Hyperosmolar Coma and Lactic Acidosis

Diabetic ketoacidosis

Summary

- Diabetic ketoacidosis is the largest single cause of death in diabetic patients under the age of 20 years in the UK, with an average mortality of about 7% of episodes. Mortality is particularly high in the elderly.
- The common precipitating causes are infection, management errors and new cases of diabetes, but there is no obvious cause in about 40% of episodes.
- Ketoacidosis is initiated by an absolute or relative insulin deficiency and an increase in catabolic hormones, leading to hepatic overproduction of glucose and ketone bodies.
- Symptoms include increasing polyuria and polydipsia, weight loss, weakness, drowsiness and eventual coma (10% of cases); abdominal pain may be present, particularly in the young.
- Signs include dehydration, hypotension, tachycardia, hyperventilation and hypothermia.
- Immediate investigations should include bedside blood glucose and ketone estimations by reagent strips, followed by laboratory measurements of blood glucose, urea, Na^+, K^+, full blood count, arterial blood pH (and gases in shocked patients), and blood and urine culture in all subjects.
- Treatment involves:

  rehydration with isotonic saline (e.g. 1 l/h for first 3 h, 6–10 l for first 24 h);

  short-acting insulin, ideally by low-dose intravenous infusion (e.g. 5–10 U/h until blood glucose level reaches 14 mmol/l, then 2–4 U/h), or by intramuscular injection (e.g. 20 U initially followed by 5–10 U/h until blood glucose reaches 14 mmol/l);

  potassium replacement (generally 20 mmol K^+ per litre of saline, adjusted by careful monitoring).
- Small doses of sodium bicarbonate (100 mmol, given as isotonic (1.4%) solution) may be given if the blood pH is <7.0 or cardiorespiratory collapse seems imminent.
- Complications of ketoacidosis include cerebral oedema (especially in the young), adult respiratory distress syndrome and thromboembolism.

Ketoacidosis is the largest single cause of death in diabetic patients under the age of 20 years in the UK and accounted for 15% of deaths in diabetic patients under the age of 50 years in a recent survey [1]. Although it principally affects younger IDDM patients, ketoacidosis may be precipitated in patients of any age during severe intercurrent illness. Although many ketoacidosis-related deaths are inevitable consequences of associated medical conditions such as overwhelming infection or myocardial infarction, others are still potentially preventable, and due to delays in presentation or diagnosis or to errors in management [1]. Despite improvements in general medical care, the incidence of diabetic ketoacidosis in Western countries has not fallen substantially in recent years [2].

Definition

The cardinal biochemical features of diabetic ketoacidosis are hyperglycaemia, hyperketonaemia and metabolic acidosis. The working definition of Alberti [3] continues to be useful: 'severe

uncontrolled diabetes requiring emergency treatment with insulin and intravenous fluids and with a blood ketone body (acetoacetate and 3-hydroxybutyrate) concentration of greater than 5 mmol/l. Few centres routinely measure ketone body concentrations and biochemical confirmation of the diagnosis is usually based on semi-quantitative methods such as Acetest or Ketostix applied to plasma.

Mortality

Before the introduction of insulin in 1923, diabetic ketoacidosis was invariably fatal. The current average mortality rate for ketoacidosis is approximately 7% although reported rates vary from 0 to 19% [4]. Although differences in defining ketoacidosis and selecting patients partly account for variation, mortality is generally higher in less specialized centres and in certain groups of patients such as the elderly [5].

In our own centre, 746 episodes of ketoacidosis were observed over a 15-year period (1971–85) in 506 patients, followed by a second episode in 47% of these patients. As in previous reports, female patients predominated, with a female to male ratio of nearly 2:1. The age distribution of the 746 episodes is given in Fig. 49.1a.

In our series, 32 patients died, producing a mortality rate of 4.3% per episode (6.3% of cases). All hospital deaths occurring in patients admitted with ketoacidosis are included in this series. Increasing age was associated with higher mortality rates (Fig. 49.1b). The principal causes of death are given in Table 49.1.

Precipitating factors

In our series, infection was the commonest identifiable cause of ketoacidosis, accounting for 207 (28%) episodes (Fig. 49.2). New cases of diabetes accounted for 10% of episodes and management errors (including inappropriate changes in insulin treatment, initiated either by patient or doctor) contributed to a further 13%. Myocardial infarction was responsible for only 1% of episodes, and miscellaneous conditions for the remaining 5%.

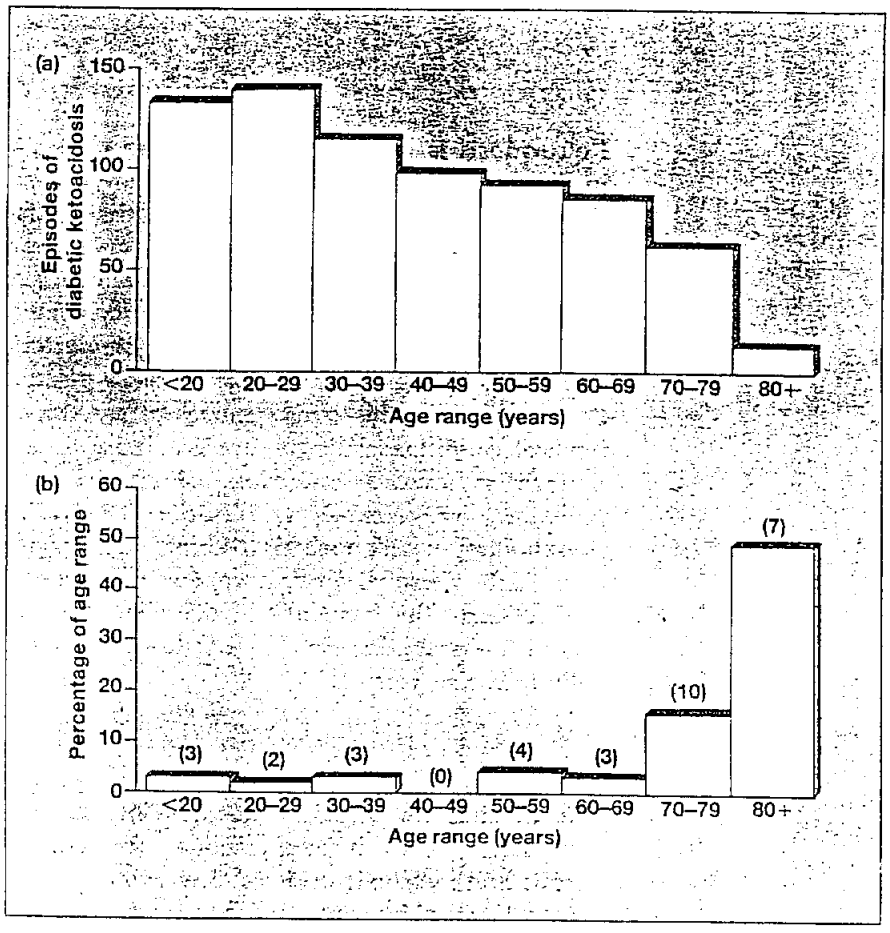


Fig. 49.1. (a) Age distribution of 746 episodes of diabetic ketoacidosis observed in Birmingham during the period 1971–85. (Paediatric cases are not represented in this series.) (b) Age distribution of deaths related to diabetic ketoacidosis (n = 32) occurring during these episodes. Numbers of deaths are shown in parentheses.

Table 49.1. Principal causes of mortality occurring in 746 episodes of diabetic ketoacidosis.

Cause of death	Number of deaths
Primary metabolic causes	10
Myocardial infarction/ congestive cardiac failure	9
Pneumonia	7
Pulmonary embolism	3
Other conditions	3
Total	32

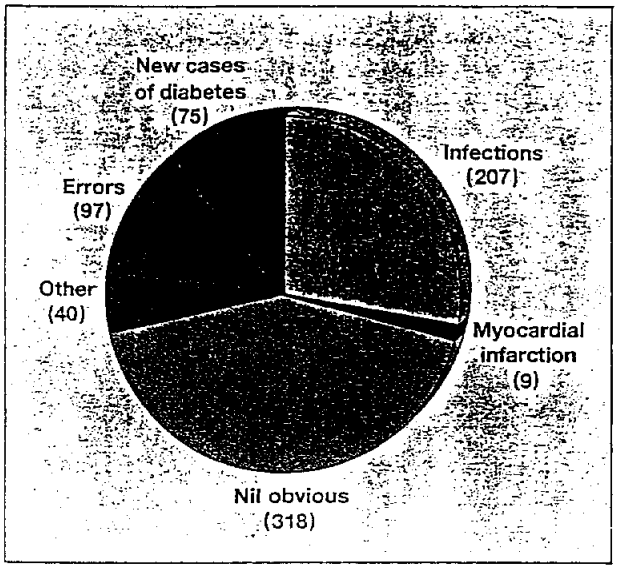


Fig. 49.2. Precipitating causes of 746 episodes of diabetic ketoacidosis observed in Birmingham during the period 1971–85.

No precipitating cause was identified in 43% of episodes.

In other centres, increased rates of ketoacidosis have been observed following initiation of continuous subcutaneous insulin infusion (CSII) [6, 7] (see Chapter 42) but ketoacidosis apparently becomes rarer as patients and clinicians become more experienced with the technique [8, 9]. Intercurrent illness, mechanical pump failure, and inadequate monitoring appear to be important factors; the small subcutaneous depot of insulin with CSII may fail to impede the development of ketoacidosis.

Pathogenesis

Diabetic ketoacidosis is characterized by increased counter-regulatory (catabolic) hormone concentrations (glucagon, catecholamines, cortisol and growth hormone), in the presence of an absolute or, more commonly, a relative deficiency of insulin [10, 11]. Although residual endogenous insulin secretion may protect against ketoacidosis in some patients [12] (Chapter 32), suppression of B-cell secretion by catecholamines during intercurrent illness may precipitate ketoacidosis in patients with NIDDM.

Withdrawal of insulin from IDDM patients leads to a rapid rise in plasma glucagon levels [13, 14] (Fig. 49.3). Dehydration and acidosis stimulate the release of catecholamines [15] and cortisol [16], producing a vicious circle in which worsening metabolic decompensation further stimulates catabolic hormone secretion.

Glucose and ketone body kinetics

Diabetic ketoacidosis is initiated primarily by hepatic overproduction of glucose and ketone bodies [17], while impaired disposal of these substrates by peripheral tissues such as muscle and brain acts to maintain the metabolic disturbance [18]. Following withdrawal of insulin from

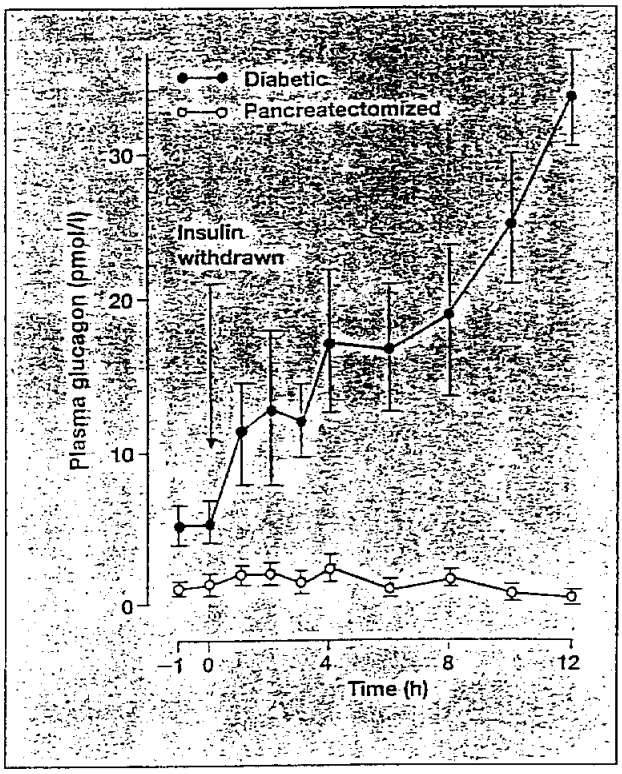


Fig. 49.3. Plasma concentrations (mean ± SEM) of glucagon in six IDDM patients and four pancreatectomized subjects after withdrawal of insulin. (Reproduced with permission from Barnes *et al.* 1977 [14].)

IDDM patients, hepatic production of glucose and ketone bodies rapidly increases (Fig. 49.4). The rate of glucose production decreases towards normal after 4 hours but hyperglycaemia is maintained because the rates of production and utilization become equal. Insulin withdrawal results in a progressive increase in both production and utilization of ketone bodies (Fig. 49.4); however, as the former always exceeds the latter, plasma ketone body concentrations rise progressively.

HYPERGLYCAEMIA

Insulin deficiency and elevated plasma levels of catabolic hormones (particularly glucagon and catecholamines) cause increased rates of hepatic glycogenolysis and gluconeogenesis. Renal gluconeogenesis is also enhanced in the presence of acidosis.

Glucose disposal by peripheral tissues such as muscle and adipose tissue is reduced by insulin deficiency while elevated plasma levels of catabolic hormones and fatty acids induce relative insulin resistance [19]. Thus, the blood glucose concentration falls more slowly during insulin treatment of patients with higher levels of catabolic hormones due to infection [20], although this degree of insulin resistance is readily overcome by 'low-dose' intravenous insulin regimens.

HYPERKETONAEMIA

Plasma ketone body concentrations are often raised to 200–300 times the normal fasting values. Ketone bodies are strong organic acids which dissociate fully at physiological pH to generate

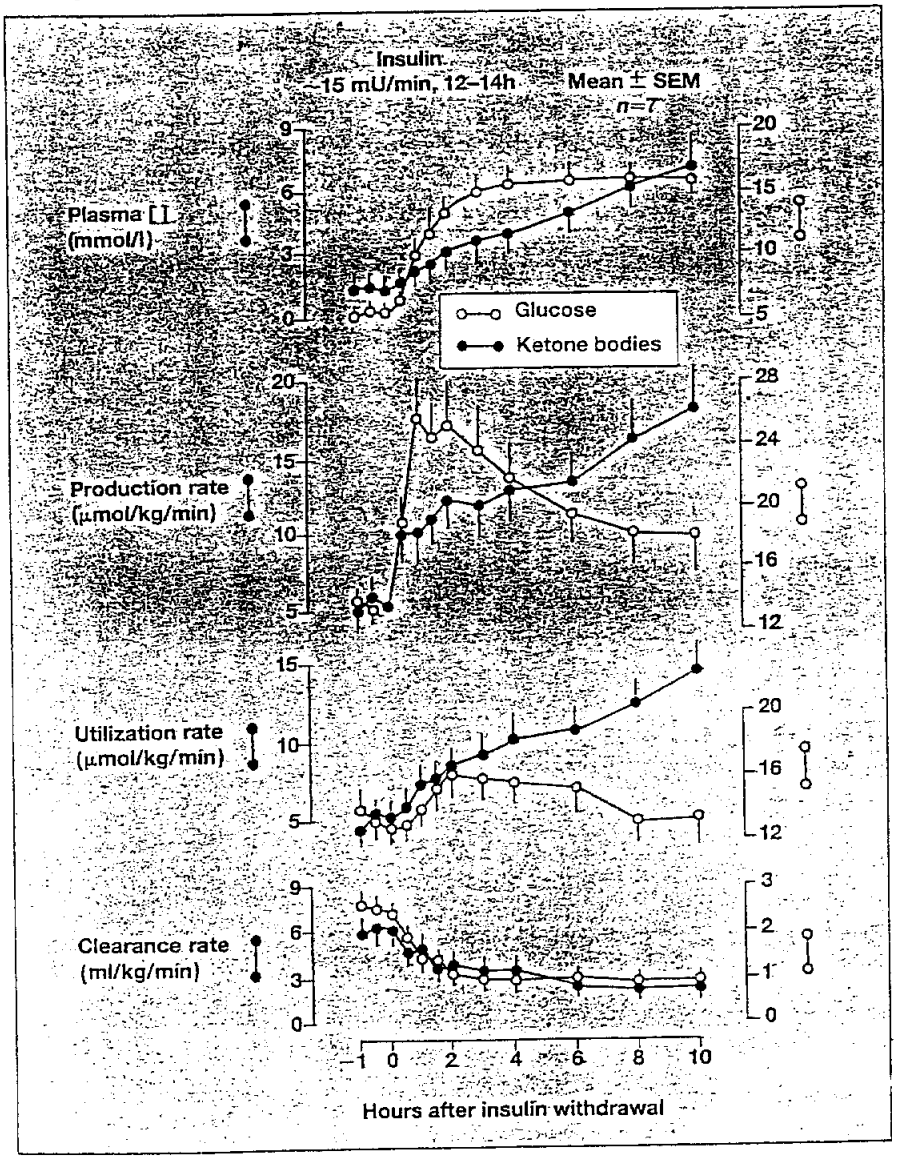


Fig. 49.4. Changes in plasma concentrations and in the rates of production, utilization and clearance of glucose and ketone bodies following withdrawal of insulin from seven IDDM patients. (Reproduced from Miles *et al.* 1980 [17] with permission of the authors and the American Diabetes Association Inc.)

equimolar amounts of hydrogen ions. Rapid rises in plasma hydrogen ion concentration in ketoacidosis outstrip the buffering capacity of the body fluids and tissues, causing metabolic acidosis which has several serious detrimental physiological effects accounting for many of the cardinal clinical features of ketoacidosis. Acidosis has a negative inotropic effect on cardiac muscle [21] and exacerbates systemic hypotension by inducing peripheral vasodilatation. The risk of ventricular arrhythmias may be increased [22] and severe acidosis (pH < 7.0) may cause respiratory depression [23]. Both ketogenesis and ketone body disposal are disturbed in ketoacidosis.

Ketogenesis. In diabetic ketoacidosis, insulin deficiency and catabolic hormone excess (particularly the catecholamines) promote excessive breakdown of adipose tissue triglyceride (lipolysis), while re-esterification is impaired, resulting in the release of large quantities of long-chain, non-esterified fatty acids. These effects are mediated via the activity of hormone-sensitive lipase, an enzyme exquisitely sensitive to inhibition by insulin.

Long-chain, non-esterified fatty acids are the principal substrate for hepatic ketogenesis, ketogenesis being directly enhanced by the increased portal delivery of fatty acids.

In diabetic ketoacidosis, concurrent with the impaired hepatic re-esterification, fatty acids are preferentially partially oxidized to ketone bodies [24]. Fatty acids are converted to coenzyme A (CoA) derivatives before transportation into the mitochondria by an active transport system (the 'carnitine shuttle'). Within the mitochondria, fatty acyl CoA undergoes β-oxidation to produce acetyl CoA which is then either completely oxidized in the tricarboxylic acid cycle, utilized in lipid synthesis, or partially oxidized to ketone bodies (acetoacetate and 3-hydroxybutyrate). The combination of insulin deficiency with elevated levels of catabolic hormones in uncontrolled diabetes strongly favours entry of fatty acids into the mitochondria and the preferential formation of ketone bodies.

Acetoacetate is in equilibrium with 3-hydroxybutyrate, according to the redox state of the liver:

$$\text{acetoacetate} + \text{NADH} + \text{H}^+ \rightleftharpoons \text{3-hydroxybutyrate} + \text{NAD}$$

(*3-hydroxybutyrate dehydrogenase*)

In ketoacidosis, the plasma 3-hydroxybutyrate: acetoacetate ratio is elevated, reflecting hepatic intramitochondrial acidosis. Acetone is formed by the spontaneous decarboxylation of acetoacetate:

$$\text{acetoacetate} \longrightarrow \text{acetone} + CO_2$$

Ketone body disposal. Most extrahepatic tissues have the capacity to utilize ketone bodies, but this is impaired in uncontrolled diabetes. Oxidation of ketone anions during treatment neutralizes the acidosis by generating bicarbonate ions. In addition, increased excretion of ketone bodies through the kidneys and lungs is important in eliminating ketone bodies in ketoacidosis.

Fluid and electrolyte depletion

Hyperglycaemia causes an osmotic diuresis when the renal threshold for glucose is exceeded, leading to dehydration and secondary losses of electrolytes [25, 26] (Table 49.2). Insulin deficiency and glucagon excess exacerbate the renal sodium depletion by impairing tubular sodium reabsorption [27]. Metabolic acidosis displaces intracellular potassium ions into extracellular fluid, which may subsequently be lost in vomit or urine. Hyperventilation, fever and sweating due to infection may further exacerbate fluid and electrolyte depletion.

In adults, average losses of body water are approximately 5 l [28]. By reducing renal blood flow, dehydration impairs a major route of elimination of glucose and ketone bodies; early in treatment, fluid replacement is therefore as important as insulin administration.

Despite a considerable total body potassium deficit (often 300–700 mmol) plasma potassium levels may be low, normal or high, although hypokalaemia at presentation signifies severe depletion of total body potassium [29].

Phosphate deficiency in ketoacidosis is associated with reduced red-cell 2, 3-diphosphoglycerate

Table 49.2. Average adult deficits of electrolytes in diabetic ketoacidosis.

Sodium	500 mmol
Chloride	350 mmol
Potassium	300–1000 mmol
Calcium	50–100 mmol
Phosphate	50–100 mmol
Magnesium	25–50 mmol

evels, which would tend to reduce oxygen delivery to the tissues [30]. However, the acidaemia of ketoacidosis partially offsets the adverse effects on the oxyhaemoglobin dissociation curve and the benefits of phosphate supplements have not been substantiated in clinical trials [31].

Clinical features

The cardinal symptoms of ketoacidosis are increasing polyuria and polydipsia, weight loss and generalized weakness, followed by drowsiness and eventually coma (Table 49.3). Symptoms usually develop over several days and all too often it is the onset of vomiting which finally precipitates emergency hospital admission.

Dehydration, hypotension and tachycardia are prominent in severe diabetic ketoacidosis. Metabolic acidosis stimulates the medullary respiratory centre, causing rapid and deep respiration (Kussmaul breathing). The odour of acetone (like 'pear drops' or nail-varnish remover) may be detectable on the patient's breath, although many people are anosmic for acetone.

Some impairment of conscious level is common, although frank coma occurs in only 10% of patients. The mechanism of ketoacidosis-induced coma remains obscure; blunting of consciousness correlates with plasma osmolarity but not with the degree of acidosis [32]. Coma at presentation is associated with a worse prognosis [33]. The possibility of coexisting causes of coma such as stroke, head injury or drug overdose should always be considered and excluded if appropriate (see Table 49.7). Acidosis causes peripheral vasodilatation which, as well as exacerbating hypotension, may lead to hypothermia, thereby masking a valuable sign of infection [34]. Rectal temperature should be checked with a low-reading thermometer if hypothermia is suspected. A non-specific leukocytosis is common in ketoacidosis and does not necessarily indicate the presence of infection.

Table 49.3. Clinical features of diabetic ketoacidosis.

Polyuria, nocturia, thirst
Weight loss
Weakness
Visual disturbance
Abdominal pain
Leg cramps
Nausea, vomiting
Confusion, drowsiness, coma

A succussion splash due to gastric stasis may be evident on abdominal examination. Generalized abdominal pain may occur in younger patients with severe acidosis [35]. If pain does not resolve within a few hours of treatment, a separate cause should be suspected; measurement of plasma amylase is unhelpful, as levels are often non-specifically raised in ketoacidosis [36].

Diagnosis and possible pitfalls

Diabetic ketoacidosis is a medical emergency. The diagnosis should be considered in any unconscious or hyperventilating patient [37] and can often be made in the casualty department following a rapid clinical examination and bedside blood and urine tests. If suspected, treatment must be started *without delay*: patients have died while waiting for laboratory confirmation of the diagnosis.

Hyperglycaemia may be rapidly determined using a glucose–oxidase reagent test strip, and urine (if available) should be tested for the presence of glucose and, most importantly, for ketones (using Acetest tablets or Ketostix dip sticks).

Venous blood is taken for laboratory measurement of glucose, urea, sodium and potassium concentrations, and a full blood count. Plasma ketone body concentrations should be measured (semi-quantitatively) using a nitroprusside-based reaction such as Ketostix or Acetest. These tests are essentially specific for acetoacetate and do not react with 3-hydroxybutyrate.

Euglycaemic diabetic ketoacidosis is recognized but is relatively uncommon [38]. Severe metabolic acidosis in the absence of hyperglycaemia (or other obvious cause of acidosis such as renal failure) raises the possibility of lactic acidosis (see later) or alcoholic ketoacidosis [39]. The latter occurs in alcoholics following a binge and reduced carbohydrate intake (often due to abdominal pain). As the metabolism of alcohol induces a more reduced hepatic mitochondrial redox state, the ratio of blood 3-hydroxybutyrate:acetoacetate is elevated, sometimes resulting in a false-negative or 'trace' Ketostix reaction despite significant ketonaemia. The same diagnostic caveat applies to lactic acidosis coexisting with ketoacidosis [40].

Despite a proportionally greater loss of body water, plasma sodium concentrations are usually normal or low, although plasma electrolyte concentrations may be falsely depressed by grossly elevated plasma glucose and lipid concentrations

in diabetic ketoacidosis [41]; conversely, plasma sodium levels may appear to rise as hyperglycaemia and hyperlipidaemia are corrected by insulin treatment. Plasma should therefore be inspected for turbidity. Eruptive xanthomata and lipaemia retinalis are rare but recognized complications of ketoacidosis, which respond to its treatment. Plasma creatinine concentration is often falsely elevated in ketoacidosis due to assay interference and may lead to an erroneous diagnosis of renal failure [42].

Acidosis is quantified by measuring capillary blood pH, Pco_2 and bicarbonate concentration. Arterial Po_2 should be measured in severely shocked patients in order to determine the degree of hypoxia [43]. Tests for sickle cell disease and G-6-PD deficiency may be indicated in selected patients.

Bacteriological culture of urine and blood (collected before antibiotics are given) is mandatory in all cases and broad-spectrum antibiotics should be given if infection is suspected. An underlying cause should be diligently sought in all patients, but investigations should not delay essential treatment or management decisions such as transfer to an intensive care unit.

Some of the potential pitfalls in the diagnosis and management of diabetic ketoacidosis are summarized in Table 49.4.

Treatment of diabetic ketoacidosis in adults

Specific treatment comprises rehydration with intravenous fluids, the administration of insulin and replacement of electrolytes. The treatment of ketoacidosis in children is considered in Chapter 87.

The importance of general medical care and close supervision of the ketoacidotic patient by trained medical and nursing staff cannot be overemphasized. A treatment flow-chart should always be employed and updated meticulously. Accurate recording of fluid balance is crucial; a urinary catheter should be inserted if no urine is passed in the first 4 hours. An initial treatment plan for diabetic ketoacidosis in adults is shown in Table 49.5.

FLUID AND ELECTROLYTE REPLACEMENT

Rehydration. Patients show considerable variation in fluid and electrolyte disturbances and the following recommendations are only a guide to therapy.

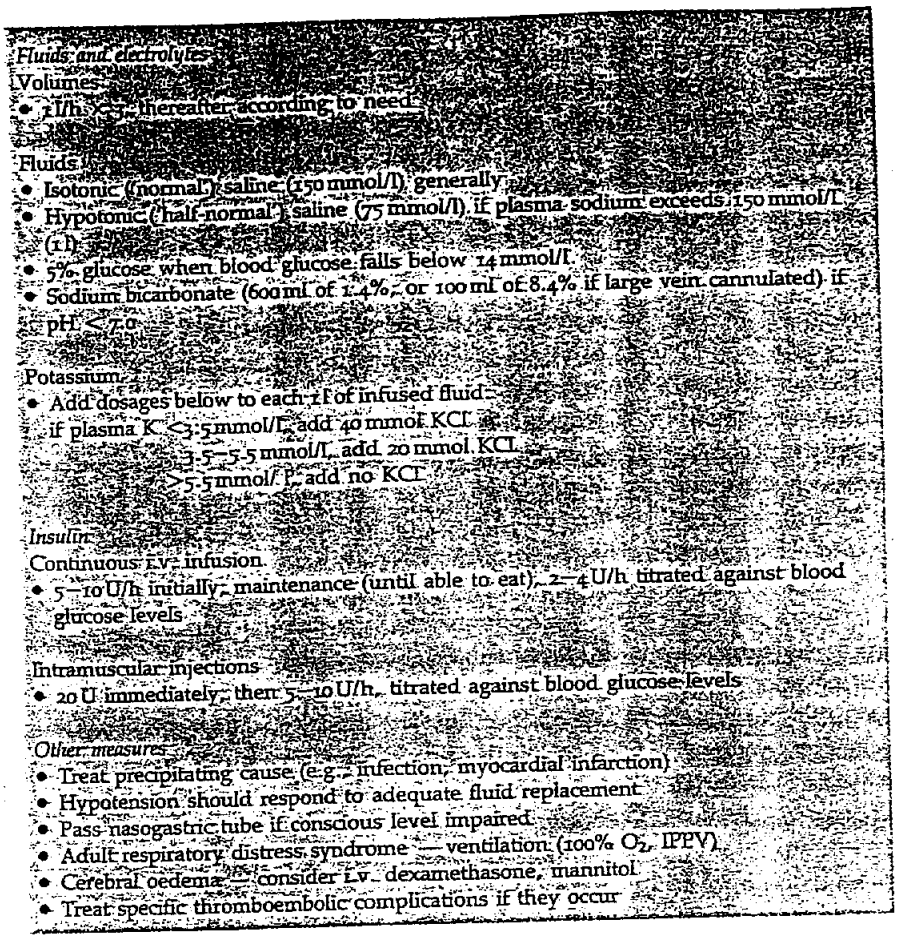
Rehydration is started with isotonic saline (150 mmol/l) containing appropriate potassium supplements (see below). Isotonic saline is used in preference to hypotonic saline (unless plasma osmolarity is significantly raised), to minimize the rapid movement of extracellular water into cells as blood glucose and osmolarity fall with treatment; such shifts have been implicated in the serious complication of cerebral oedema, discussed below.

Rehydration of the patient must take account of continuing polyuria and 6–10 l of fluid are commonly required during the first 24 h. In an average adult, 1 l of saline is infused every hour for the first 3 h. The rate of infusion is then adjusted according to the patient's clinical state. Considerable care is required in elderly patients or those with cardiac disease, in whom monitoring of central venous or pulmonary wedge pressure is strongly recommended. Occasionally, patients with relatively low plasma glucose concentrations on admission may require a simultaneous infusion of glucose.

Severe hypernatraemia (plasma sodium concentration exceeding 150 mmol/l) may necessitate

Table 49.4. Potential pitfalls in the diagnosis and management of diabetic ketoacidosis.

- *Smell of 'ketones' (acetone) on the breath:* may be absent (many people are anosmic for acetone)
- *Fever:* may be absent (peripheral vasodilation causes cooling)
- *Leukocytosis:* neutrophil count may be non-specifically raised
- *Plasma sodium concentration:* may be artificially lowered initially by high lipid and glucose levels and may appear to rise suddenly after insulin treatment lowers plasma glucose and lipid levels
- *Plasma potassium concentration:* may be temporarily raised (by acidosis) despite severe total body potassium depletion
- *Plasma creatinine concentration:* may be falsely elevated (assay interference)
- *'Ketostix' testing:* may show negative or trace result when diabetic ketoacidosis and either lactic acidosis or alcoholic ketoacidosis coexist (predominance of 3-hydroxybutyrate)



Fluids and electrolytes

Volumes

- 1 l/h ×2, thereafter according to need

Fluids

- Isotonic ('normal') saline (150 mmol/l) generally
- Hypotonic ('half-normal') saline (75 mmol/l) if plasma sodium exceeds 150 mmol/l
- 5% glucose when blood glucose falls below 14 mmol/l
- Sodium bicarbonate (600 ml of 1.4%, or 100 ml of 8.4% if large vein cannulated) if pH <7.0

Potassium

- Add dosages below to each 1 l of infused fluid

if plasma K <3.5 mmol/l, add 40 mmol KCl

3.5–5.5 mmol/l, add 20 mmol KCl

>5.5 mmol/l, add no KCl

Insulin

Continuous I.V. infusion

- 5–10 U/h initially, maintenance (until able to eat) 2–4 U/h titrated against blood glucose levels

Intramuscular injections

- 20 U immediately, then 5–10 U/h, titrated against blood glucose levels

Other measures

- Treat precipitating cause (e.g., infection, myocardial infarction)
- Hypotension should respond to adequate fluid replacement
- Pass nasogastric tube if conscious level impaired
- Adult respiratory distress syndrome — ventilation (100% O_2, IPPV)
- Cerebral oedema — consider I.V. dexamethasone, mannitol
- Treat specific thromboembolic complications if they occur

Table 49.5. Initial treatment plan for diabetic ketoacidosis in adults.

the temporary replacement of isotonic saline with hypotonic saline (75 mmol/l) or 5% glucose (with an appropriate increase in the dose of insulin).

When the plasma glucose level has fallen to about 14 mmol/l, 5% dextrose solution is administered at a rate of around 250 ml/h until the patient is eating again, in order to avoid hypoglycaemia. The use of hypertonic (10%) glucose at this stage of treatment appears to confer no clinical advantage over 5% glucose [44].

Potassium replacement. Cardiac arrhythmias induced by iatrogenic hypokalaemia represent a major and avoidable cause of death. Insulin treatment and rising pH cause extracellular potassium to enter cells and, on average, 20 mmol of potassium (administered as 1.5 g potassium chloride) will be required in each litre of fluid following the start of insulin therapy. Continuous ECG monitoring may indicate signs of hypo- or hyperkalaemia, but the serum potassium concentration must be checked regularly (2-hourly at first) and potassium supplements adjusted appropriately. Particular care must be exercised in patients with renal failure, anuria or oliguria (urine output less than 40 ml/h). If hypokalaemia is present (plasma potassium <3.5 mmol/l), potassium supplements should be doubled to 40 mmol per litre of infused fluid; if hyperkalaemia develops, potassium should be temporarily withheld.

INSULIN THERAPY

The aims of insulin treatment in ketoacidosis are to inhibit lipolysis (and thus ketogenesis) and hepatic glucose production and to enhance the disposal of glucose and ketone bodies by peripheral tissues.

As short-acting insulin has a plasma half-life of only about 5 min [45], intermittent injections produce unpredictable and fluctuating plasma insulin concentrations. Maximal stimulation of potassium transport into cells occurs at pharmacological plasma insulin concentrations [46] and large doses of insulin therefore increase the risk of hypokalaemia. With current 'low-dose' insulin regimens, complications of treatment such as hypokalaemia and late

hypoglycaemia are less common than with the obsolete 'high-dose' regimens [47].

Short-acting insulin (e.g. Human Actrapid (Novo), Human Velosulin (Nordisk) or Humulin S (Lilly)) is best administered as a continuous intravenous infusion at a rate of 5–10 U/h. This produces steady plasma insulin concentrations in the high physiological range which adequately suppress lipolysis, ketogenesis and hepatic glucose production, even in the presence of elevated levels of catabolic hormones. Insulin is diluted to a convenient concentration (usually 1 U/ml) with isotonic saline in a large syringe and delivered by a syringe-driver infusion pump connected via a Y-connector. The infusion apparatus should be flushed through before connection to the patient in order to prevent insulin from adsorbing on to the plastics. Alternatively, insulin may be diluted in a 500-ml bag of isotonic saline; the insulin must be injected using a needle long enough to clear the injection port of the bag, and a few millilitres of the patient's plasma or whole blood can be added to discourage insulin adsorption (see Figs 81.1 and 81.2).

With intravenous regimens, blood glucose is checked at the bedside at hourly intervals and the infusion rate is reduced to 2–4 U/h when glucose has fallen to 14 mmol/l or below. The blood glucose concentration should then be maintained at between 5–10 mmol/l until the patient is eating and subcutaneous insulin is recommenced.

If intravenous insulin administration is impracticable, an intramuscular regimen can be used. This begins with a bolus of 20 U short-acting insulin, followed by 5–10 U each hour until blood glucose (checked hourly at the bedside) has reached 14 mmol/l. Subcutaneous insulin is commenced at this time, with the start of a 5% dextrose infusion, at a dosage of 10 U 4-hourly and continued for about 24 hours, when the patient's usual insulin regimen is reintroduced.

Both intravenous and intramuscular regimens should produce a steady and predictable fall in plasma glucose concentrations, averaging 4–6 mmol/h [48]. The commonest causes of failure to respond to intravenous insulin are the pump being inadvertently switched off or set at the wrong rate, and blockage of the delivery line. Insufficient rehydration has been said to cause erratic absorption of intramuscular injections, resulting in apparent insulin resistance. If the plasma glucose concentration has not fallen after 2 hours of intramuscular treatment, the patient's fluid balance should be reappraised and intravenous insulin started.

BICARBONATE

The place of bicarbonate in the management of diabetic ketoacidosis remains controversial [49]. Blood pH levels below 7.0 may lead to life-threatening respiratory depression and small doses of bicarbonate (approximately 100 mmol) may be beneficial if the patient is severely acidotic or if cardiorespiratory collapse appears imminent. However, it is possible that administration of bicarbonate to the *extracellular* space may actually aggravate *intracellular* acidosis. Bicarbonate ions (which cannot diffuse across cell membranes) combine with H^+ ions extracellularly, producing carbonic acid which dissociates into water and CO_2. The latter readily enters cells, where the reverse reaction occurs, generating H^+ (and bicarbonate) ions intracellularly.

Bicarbonate should be infused as 100 ml of 8.4% solution or 600 ml of 1.4% solution over 30 min and repeated if necessary to raise the pH above 7.0. Complete correction of the acidosis should not be attempted as concurrent metabolism of ketone anions may lead to over-alkalinization.

Administration of alkali is associated with a number of potentially serious adverse effects including hypokalaemia, paradoxical acidosis of cerebrospinal fluid [50], adverse effects on the oxyhaemoglobin dissociation curve [51], overshoot alkalosis [52] and a delayed fall in lactate and ketone body concentrations [53]. Extra potassium (20 mmol potassium per 100 mmol bicarbonate) must always be administered when bicarbonate is infused. A solution of 8.4% sodium bicarbonate is extremely irritant and because of its tendency to cause thrombosis should only be infused into a large (ideally central) vein; extravasated solution often causes extensive local tissue necrosis (see Fig. 49.5).

OTHER MEASURES

The stomach of a patient with diabetic ketoacidosis may contain 1–2 l of fluid which can be vomited and inhaled if consciousness is blunted, occasionally with fatal results. Although attempts to pass a nasogastric tube may precipitate vomiting in uncooperative patients, this should be done (by an experienced person) if there is

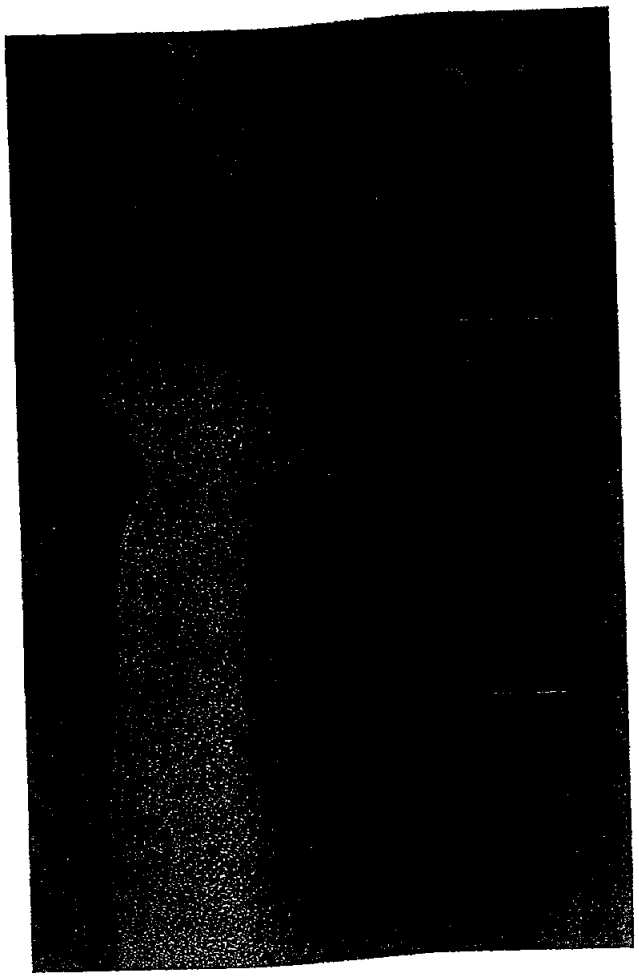


Fig. 49.5. Extensive necrosis of superficial tissues, which required skin grafting, following extravasation of 8.4% sodium bicarbonate solution.

any nausea or vomiting in a patient who is not fully awake.

It is generally suggested that persistent hypotension (<80 mm Hg systolic) should be treated with plasma expanders, but we have not required this in our last 746 episodes of ketoacidosis and consider it unnecessary, as long as general rehydration is adequate.

Complications of diabetic ketoacidosis

CEREBRAL OEDEMA

Cerebral oedema is a rare and poorly understood cause of death in diabetic ketoacidosis which appears to have a predilection for younger patients [54]. Characteristically, the patient initially responds well to treatment but then develops neurological signs and deepening coma.

Subclinical elevations in cerebrospinal fluid pressure are common during the treatment of ketoacidosis, due to alterations in cerebral osmolarity [55]. Cerebral swelling has been demonstrated in children using computerized tomography [56] (see Fig. 87.7). Animal experiments suggest that rapid reductions of plasma glucose concentration to below 14 mmol/l may contribute to cerebral oedema [57], although it is difficult to find support for this view in case reports. The use of hypotonic fluids during treatment has also been implicated [58, 59] but the evidence is again inconclusive. No fatalities attributable to cerebral oedema occurred in the 746 episodes of ketoacidosis treated in our centre between 1971 and 1985, although paediatric cases are not represented in this series. Dexamethasone and/or mannitol are often suggested in the treatment of cerebral oedema, but there is no firm evidence that either is beneficial.

ADULT RESPIRATORY DISTRESS SYNDROME

The adult respiratory distress syndrome (ARDS) has recently been reported as a major cause of death in younger patients with ketoacidosis. Clinical features include dyspnoea, tachypnoea, central cyanosis and non-specific chest signs. Arterial hypoxia is characteristic and chest radiography reveals bilateral pulmonary infiltrates. Management involves respiratory support with intermittent positive pressure ventilation (IPPV) and avoidance of fluid overload. Corticosteroids do not seem to have a useful place in the treatment of ARDS.

THROMBOEMBOLISM

Thromboembolic complications, due to dehydration and increased blood viscosity and coagulability, are an important cause of mortality in diabetic ketoacidosis [61]. Disseminated intravascular coagulation has also been reported as a rare complication of diabetic ketoacidosis [62].

The role of prophylactic anticoagulation has not been clearly established in diabetic ketoacidosis but does not improve survival in hyperosmolar coma where thromboembolic complications are common; routine anticoagulation is therefore not recommended, although proven thromboembolic disease should be treated in the usual way.

Diabetic non-ketotic hyperosmolar coma

Summary

- Non-ketotic hyperosmolar coma is characterized by the insidious development of marked hyperglycaemia (usually >50 mmol/l) and dehydration and pre-renal uraemia; significant hyperketonaemia does not develop.
- The absence of ketosis is unexplained but may be related to suppression of lipolysis by hyperosmolarity, or a reduced catabolic hormone response.
- Two-thirds of cases are in previously undiagnosed cases of diabetes. Infection, diuretic treatment, and drinking glucose-rich beverages may all be precipitating factors.
- The condition usually affects middle-aged or elderly patients and carries a mortality of over 30%.
- Treatment involves rehydration, insulin therapy and electrolyte replacement in a manner similar to that used for diabetic ketoacidosis.

Pathophysiology

Diabetic hyperosmolar non-ketotic coma is characterized by marked hyperglycaemia (plasma glucose usually in excess of 50 mmol/l), with profound dehydration, pre-renal uraemia and depressed consciousness [63]. Gross hyperketonaemia and ketonuria are absent.

Insulin concentrations in peripheral blood are similar to those in patients with ketoacidosis [64, 65] and the absence of significant ketosis is unexplained. Suppression of lipolysis by the hyperosmolar state is one suggested mechanism [66]; the catabolic hormone response may also be less marked than in patients with ketoacidosis [64, 67].

Incidence and mortality

In our own centre, 95 cases of hyperosmolar non-ketotic decompensation occurred in 89 patients between 1971–85, accounting for about 11% of hyperglycaemic emergencies. The mortality rate for our patients was 31% per 100 episodes (33% per 100 patients). The condition's high mortality reflects the high incidence of serious associated disorders and complications [68].

Clinical features

Patients with hyperosmolar non-ketotic decompensation are usually middle-aged or elderly [60, 69]. Patients of Afro-Carribean origin accounted for 26% of episodes of hyperosmolar non-ketotic decompensation in our series, compared with only 3% of episodes of ketoacidosis. Up to two-thirds of cases occur in patients with previously undiagnosed diabetes [68]. Hypertension and treatment with diuretics are well-recognized features.

Symptoms of polyuria, intense thirst and gradual clouding of consciousness are characteristic. Many patients drink carbonated glucose drinks, which only exacerbate thirst and hyperglycaemia. The symptoms may develop over several weeks. Coma and severe dehydration with arterial hypotension are common and reversible focal neurological signs or motor seizures may occur [70]. Kussmaul respiration is not a feature of the hyperosmolar non-ketotic state as significant acidosis is absent. Many patients are moribund when admitted to hospital.

Precipitating factors

Hyperosmolar non-ketotic coma has many precipitating causes, which often coexist in one patient [71]. Infections are frequent and hyperosmolar coma may follow treatment with antihypertensive drugs such as diuretics and β-blockers [72, 73]. Steroids, phenytoin and cimetidine have also been associated with hyperosmolar coma. The possible contribution of glucose-rich drinks has already been mentioned.

Diagnosis

The insidious nature of the condition often leads to delays in diagnosis; an erroneous diagnosis of stroke is commonly made. Hyperosmolar non-ketotic coma must therefore enter the differential diagnosis of any patient presenting with otherwise unexplained impairment of consciousness, focal neurological signs, dehydration or shock [74].

Urinalysis reveals glycosuria and a negative or 'trace' reaction with Ketostix. The diagnosis is confirmed by a markedly raised plasma glucose concentration. Pre-renal uraemia and a raised

haematocrit are common. Depression of consciousness generally occurs when plasma osmolarity exceeds about 340 mosmol/l [75], although there is considerable inter-individual variation [76]. Plasma osmolarity can be measured formally (e.g. by freezing-point depression) in the laboratory, and can be estimated approximately as:

plasma osmolarity (mosmol/l) = 2 × (plasma Na + plasma K) + plasma glucose + plasma urea

(Na, K, glucose and urea concentrations are in mmol/l).

Treatment

Successful management of hyperosmolar non-ketotic coma depends on good general care of the unconscious patient and prompt recognition and treatment of underlying causes.

Fluid, electrolyte and insulin replacement are similar to those recommended for the treatment of diabetic ketoacidosis [77]. Isotonic saline is used in preference to hypotonic saline for rehydration unless plasma sodium exceeds 150 mmol/l. A rise in sodium is frequently observed as blood glucose falls with treatment. This observation may be partially explained by the reciprocal relationship that exists between plasma glucose and sodium concentrations [78].

Despite the high frequency of thromboembolic complications in patients with hyperosmolar non-ketotic coma, the role of routine anticoagulation remains unclear [79], and it is probably best to treat thromboembolic disease only if it occurs. Neurological signs usually reverse when hyperglycaemia is controlled; epilepsy also responds to insulin and fluid replacement, but often not to specific anti-epileptic drugs [80].

Although insulin treatment is usually recommended for the first few months, these patients generally secrete significant quantities of endogenous insulin, allowing successful long-term treatment with oral hypoglycaemic agents [81]. Possible precipitating factors (thiazides, glucose drinks) must be carefully avoided in the future.

Lactic acidosis

Summary

- Severe lactic acidosis in diabetic patients (type B) occurs as a feature of ketoacidosis (in about 15% of cases) and as a rare complication of metformin therapy.
- When associated with ketoacidosis, lactic acidosis resolves with standard treatment of the ketoacidosis, that due to other causes may be treated by intravenous sodium bicarbonate.
- Sodium dichloroacetate, which lowers lactate levels by stimulating pyruvate dehydrogenase, is a potential new treatment for lactic acidosis, but clinical experience with this agent is limited to date.

The principal organs producing lactic acid are skeletal muscle, brain, erythrocytes and the renal medulla. The liver, kidneys and heart normally *extract* lactate but may become net producers of lactic acid under conditions of severe ischaemia [82]. Lactate produced by glycolysis is either oxidized to CO_2 and water or utilized in the gluconeogenic pathway in the liver and kidney (the Cori cycle).

Pathological degrees of lactic acidosis may arise from overproduction of lactate and hydrogen ions, a decrease in their clearance or a combination of

Table 49.6. Classification and causes of lactic acidosis. (Modified from Cohen and Woods 1976 [85]).

Type A (Primarily associated with tissue hypoxia)
Shock:
Cardiogenic
Endotoxic
Hypovolaemic
Cardiac failure
Asphyxia
Carbon monoxide poisoning
Type B
1. Systemic disorders:
Diabetes mellitus
Neoplasia
Liver disease
Convulsions
2. Drugs and toxins:
Biguanides
Ethanol
Methanol
Salicylates
Fructose/sorbitol/xylitol (in parenteral nutrition)
3. Inborn errors of metabolism

these two processes. Normal fasting blood lactate concentrations range from 0.4–1.19 mmol/l [83]. Severe lactic acidosis (defined as a metabolic acidosis with a blood lactate concentration of greater than 5 mmol/l) is encountered in two main clinical settings [84] (Table 49.6):

Type A lactic acidosis is primarily associated with states of tissue hypoxia such as shock or cardiac failure.

Type B lactic acidosis is considerably less common and is associated with several systemic diseases including diabetes, drugs, toxins and inborn errors of metabolism (e.g. Type 1 glycogen storage disease). Tissue hypoxia is not an obvious feature of type B lactic acidosis, although hypotension and hypoxia may supervene as preterminal events. The clinical features of lactic acidosis are similar to those of a severe metabolic acidosis of any cause.

Lactic acidosis associated with diabetes

Despite the frequent macrovascular and microvascular complications which favour tissue hypoxia, severe lactic acidosis is only rarely associated with diabetes [85]. Type B lactic acidosis is a well-recognized complication of biguanide therapy (Chapter 48) and a significant degree of hyperlactataemia is relatively common in diabetic ketoacidosis.

BIGUANIDE THERAPY

The incidence of lactic acidosis in diabetic patients has declined dramatically since the withdrawal of the biguanide, phenformin, in 1977 [86]. Lactic acidosis associated with phenformin treatment carried a 50% mortality rate [87]; lactic acidosis complicating metformin therapy is now rare and occurs almost exclusively in patients in whom biguanide therapy is contraindicated [88].

Many diabetic patients treated with insulin or biguanides show daily fluctuations in blood lactate concentration of up to 3 mmol/l [89].

DIABETIC KETOACIDOSIS

Significant hyperlactataemia is found in 15% of cases of diabetic ketoacidosis and usually responds to routine treatment of the ketoacidosis [89]. It is difficult to know whether this is a true mixed picture of lactic and ketoacidosis or simply an effect upon redox potential of the hydrogen ions generated in ketoacidosis. Resolution with treatment of ketoacidosis favours the latter explanation as insulin–glucose infusions are ineffective in the treatment of lactic acidosis.

It is not surprising that rises in blood lactate concentration occur when treatment of ketoacidosis is instituted. Insulin suppresses gluconeogenesis, thus reducing hepatic extraction of lactate from the blood, while facilitating peripheral glucose uptake and metabolism and therefore promoting lactate generation. This rise in lactate is generally transient and insignificant but massive rises in lactate were seen during the treatment of ketoacidosis treatment with the now-obsolete high-dose insulin regimens [90]. Hyperlactataemia also follows primary hypoxia, when it represents a preterminal event. Treatment is directed at the underlying cause of the hypoxia.

Treatment and prognosis

The generally poor prognosis associated with lactic acidosis is largely determined by the severity of the underlying condition. Despite considerable controversy surrounding the theoretical and clinical benefits of alkali therapy, intravenous bicarbonate remains the mainstay of supportive treatment for cases of severe lactic acidosis [91]. Massive quantities of bicarbonate may be required to elevate arterial pH, and simultaneous dialysis has been recommended to avoid sodium overload [92].

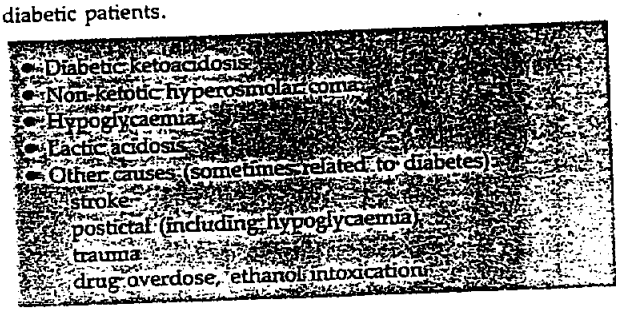
Sodium dichloroacetate has recently received attention as a potential adjunct in the management of lactic acidosis [93]. By stimulating the activity of pyruvate dehydrogenase, dichloroacetate lowers blood lactate levels in patients with lactic acidosis associated with a variety of conditions [94]. To date, clinical experience with this compound remains limited and there is no evidence that the overall prognosis is improved.

Finally, hyperglycaemia may induce generalized epileptic convulsions in susceptible patients causing a severe but self-limiting lactic acidosis. In such cases, bicarbonate therapy is both unnecessary and potentially hazardous [95].

Differential diagnosis of coma in a diabetic patient

The commonest causes of impaired consciousness in diabetic patients presenting to hospital casualty departments in the UK are ketoacidosis, hypoglycaemia and hyperosmolar, non-ketotic coma.

Table 49.7. Causes of coma or impaired consciousness in diabetic patients.



However, it is essential to remember that diabetic people, like anyone else, may suffer other causes of coma, some of which may be associated with diabetes or its treatment (see Table 49.7).

Immediate measurement of the blood glucose concentration (using a glucose–oxidase reagent strip rather than waiting for a formal laboratory result) is mandatory and will usually determine the initial course of treatment, which can often be started while awaiting more detailed laboratory results. The diagnostic criteria for the metabolic causes of coma in diabetes are described in the relevant sections above. It must be appreciated that lactic acidosis or a hyperosmolar state may each complicate diabetic ketoacidosis, and that (for example) unconsciousness may follow a generalized epileptic seizure provoked by hypoglycaemia or a head injury sustained during a hypoglycaemic attack.

A.J. KRENTZ

MALCOLM NATTRASS

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27 April 2003

Mrs Jennie Chok,

Government Secretariat,

Lower Albert Road,

Hong Kong.

Your ref: SBCR 2/3/2856/96

Dear Mrs Chok,

Re: Death Inquest CCDI-2139/2001 Prisoner CHEUNG Chi-kin

I am writing to you at Professor Karen SL Lam's request to provide you with further information regarding the questions you set out in Annex B in your letter of 28 March 2003. I shall focus on clinical pharmacological issues and confine my comments to

chlorpromazine. My responses to your questions are as follows:

Could chlorpromazine be built up and sequestered in the tissues and human fat gradually without causing any overt symptoms of the deceased?

Chlorpromazine is fat soluble and can be sequestered in tissues and human fat. The concentration of chlorpromazine in the brain for example, can be ten times higher than the concentration in the blood. The response to chlorpromazine is highly variable and there may not be any apparent effects.

Could any normal person survive if the blood chlorpromazine level is around 9.7 microgram/millilitre? What would be the lethal level of the drug on normal person? Is it possible that the deceased with the detected drug level had adapted to the drug to the extent that he could bear such high drug level in his blood and survive for 40 hours in SLPC before death?

A blood chlorpromazine level of around 9.7 microgram/milliliter is more than ten times the usual therapeutic level. It is certainly in the toxic range. It would be dangerous,

but I would not like to speculate if this is definitely lethal or not. In the literature, there was a person who took 10g of chlorpromazine and still survived. Chlorpromazine is often said to be a relatively safe drug. It has a large safety margin – the lethal dose being two hundred times the normal dose. Although a high blood level of chlorpromazine may not cause immediate death, it may still be life threatening. For example, it might cause low blood pressure, depress respiration, or cause convulsions, all of which require supportive medical treatment for survival. Once the subject is receiving medical care, the outlook for recovery is excellent.

Although I speculated that one could survive a high concentration of chlorpromazine, it is unlikely that such a high level would not be accompanied by toxic manifestations. I think it unlikely that the deceased had this high level all along and had adapted to it.

If such a large dose of chlorpromazine causing the fatal outcome of the deceased had been administered to the deceased before admission to SLPC, could he manage to survive for 40 hours in the Centre?

If it is assumed that the chlorpromazine level of 9.7 microgram/millilitre caused death,

then it is unlikely that it only triggered death after 40 hours. The blood level of a drug usually decreases with time after it has been absorbed and distributed. In the case of chlorpromazine, it is metabolised or broken down in the liver and these metabolites are excreted in the urine. Therefore, over the time scale of 40 hours, one would normally expect that there would be decreasing amount of drug in the body. It is conceivable, however, that whilst the total amount of drug in the body is decreasing slowly, lipolysis might have released a large amount of chlorpromazine and that might elevate the blood level of chlorpromazine and might have contributed to death. However, this is only theoretical.

Is it possible that the chlorpromazine blood level being accumulated up to 9.7 microgram/milliliter was subsequent to the lipolysis which was indicated by the ketoacidosis and fat decomposition during the post-mortem changes of the deceased, causing the drastic reduction in body weight of 19 kg of the deceased in five days?

As mentioned above, this is theoretically possible. On the other hand, a weight loss of 19 kg is remarkable. The weight loss in this case, would involve both the loss of fluid and fat, as a result of osmotic diuresis consequent to the hyperglycemia and accelerated

lipolysis respectively.

If the deceased had died because of the adverse effect of chlorpromazine, then how long before death might it have been administered?

I cannot give an answer to this question on the basis of one drug level. This has to be determined from the medical history and from investigations and inquiries.

Given the level of chlorpromazine of 9.7 microgram/milliliter in the blood, if the drug was taken within a short period of time, how much drug (both taken orally or administered by injection) would need to be taken to cause such readings?

There is no definite answer to this question. Patients taking the drug regularly have blood levels of chlorpromazine of 30 to 350 nanogram/millilitre, but it does not necessarily mean that the deceased must have taken 30 to 300 times the normal dose. The absorption, distribution and metabolism of the drug are highly variable in different people. Again, there is the possibility of drug released by lipolysis and post-mortem redistribution.

One can perform a highly theoretical calculation of dose by making a series of assumptions. If we take, for convenience, 10 microgram/millilitre (= 10 milligram/litre) as the blood concentration in a living person, then assuming that the volume of distribution is 20 litres, there are 200 milligrams of the drug in the body. Not all the drug is absorbed in the gut. Commonly, only 30% or so is absorbed. Furthermore, the drug is constantly being broken down and eliminated. Therefore in theory, the dose of chlorpromazine should be in excess of 500 milligrams.

Can chlorpromazine cause the adverse effect of priapism? Is there any preparation of drugs with ingredients of phenothiazine which can enhance the sexual performance of the subject as well as can be obtained over the counter easily?

Chlorpromazine has been reported to be associated with priapism. This is not a common and predictable side effect. The more usual effect is one of causing sexual dysfunction. Nowadays, Viagra would be a more effective choice to facilitate erection.

Are there any drugs (whether registered or not) which, after intake, would produce the chlorpromazine metabolite blood level on post-mortem examination?

Chlorpromazine is not a metabolite of other phenothiazines used in clinical practice. Chlorpromazine itself is metabolised to a number of metabolites some of which are inactive and some active. The answer to the question lies in how precise the analytical method is in distinguishing chlorpromazine from other substances. As to the possibility of false positives due to a substance that has similar chemical characteristics, the government chemist can clarify this.

Could we say that the hyperglycaemia and ketoacidosis had caused the death of the deceased in the situation whereas the cause of having lethal level of chlorpromazine was secondary to the lipolysis and post-mortem redistribution on the deceased?

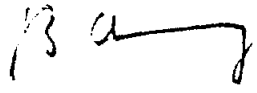
Diabetic ketoacidosis is a highly dangerous condition, which if unrecognised and untreated, very likely leads to death. On the other hand lipolysis and post-mortem redistribution could also have markedly increased the level of chlorpromazine in the post-mortem blood.

Regardless of the possible post-mortem redistribution leading to further elevation of the chlorpromazine blood level, would the adverse effect of chlorpromazine released through lipolysis be the main cause of the death? Or, is it possible that both the complication of ketoacidosis and adverse effect of chlorpromazine had contributed to the death of Mr Cheung?

The chlorpromazine that is released through lipolysis and enters the circulation may also be a cause of death, or a contributory cause.

I would be delighted to elaborate further on the above points if you wish.

Yours sincerely,



Bernard Cheung

Dr Bernard M Y Cheung, MA, MBBChir, PhD(Cantab),

MRCP(UK), FRCP, FRCPE, FCP, FHKCP, FHKAM(Medicine),

Associate Professor,

Division of Clinical Pharmacology,

Department of Medicine, The University of Hong Kong,

[redacted]

[redacted]

Tel: [redacted] Fax: [redacted]

Email: [redacted]

5 July 2003

Mr David Wong,

Principal Assistant Secretary,

Security Bureau,

Government Secretariat,

Lower Albert Road,

Hong Kong.

Dear Mr Wong,

Re: Death Inquest CCDI-2139/2001 Prisoner CHEUNG Chi-kin

Thank you for sending me photographs of the deceased at autopsy, for the purpose of commenting on the presumed needle marks over the right shoulder.

Given the limitations of making deductions from photographs, I am prepared to state that the three marks on the right shoulder and the associated bruises could be the result of attempted cannulation of the right cephalic vein. The three puncture sites overlie the course of the right cephalic vein, which ascends the right arm, lies in the groove between the deltoid muscle and the pectoralis major muscle, before penetrating deeply to join the axillary vein under the right collar bone. It is not the commonest site used for venous access, but can be used if more peripheral veins in the forearm or elbow are not accessible.

I would be delighted to elaborate further on the above points if you wish.

Yours sincerely,

Bernard Cheung

cc Prof KSL Lam

Death Inquest CCDI-2139/2001
Prisoner CHEUNG Chi-kin

1. I am Prof. LEE Kwing-chin, Kenneth. I have been requested by the Security Branch of the Government to give expert opinion in the inquest of the above court case. It is my understanding that my opinions expressed will be used at the upcoming meeting of the Security Panel and the Health Services Panel of the Legislative Council. If deemed appropriate, the matter will be taken further for an application to the Court of First Instance to re-open the death inquest.

2. My present employment is at School of Pharmacy, Faculty of Medicine, the Chinese University of Hong Kong; in the position of Professor and Head, Division of Pharmacy Practice. I am also Honorary Senior Lecturer at the School of Pharmacy, University of London (Please refer to my attached CV in Annex A for other details). I have previously provided expert opinion in over 10 court cases in relation to prosecution of drug trafficking, death inquiries of drug abusers and other criminal offences.

3. For the present report, my major responsibilities are:

   a. To provide an explanation regarding the abnormally high post-mortem blood levels of chlorpromazine and methadone in the deceased based on the standard principles of pharmacokinetics (PK),
   b. Based on the deduction arising from (a), to provide views from an angle of an independent expert as to whether the afore-said medications were related to the death of the deceased.

4. My report is divided accordingly into the following parts:
   a. Introduction on the subject of PK and the drugs chlorpromazine and methadone with special reference to their PK characteristics
   b. Discussion on the results arising from the PK calculations
   c. Summary and conclusion

INTRODUCTION

5. Pharmacokinetics is a study discipline of health science to study and hence to understand the relationship between the physicochemical properties of a drug and the pharmacologic or clinical effect. A general scheme of this dynamic relationship is described in Figure (1).

6. Measurement of drug concentration in the blood, serum, or plasma is the most direct approach to assess the PK of the drug in the body. The intensity of the pharmacologic as well as toxic effect of a drug is often related to the concentration of the drug in the blood.

7. Drugs are constantly in a dynamic state within the body. In order to describe a complex biologic system, simplifying assumptions are often made concerning the

movement of drugs. Various mathematical models are hence designed to simulate the rate processes of drug absorption, distribution and elimination. These mathematical models make possible the development of equations to describe the change in drug concentrations in the body as a function of time.

8. PK models can be used in the following situations:[2]

   a. Predict plasma drug levels with any dosage regimen
   b. Calculate the optimum dosage regimen for each individual patient
   c. Estimate the possible accumulation of drugs
   d. Correlate drug concentrations with pharmacologic or toxicologic effects
   e. Evaluate the differences between different formulations of the same drug
   f. Describe how changes in physiology of the body affect the absorption, distribution, or elimination of the drug
   g. Explain drug interactions

Chlorpromazine

9. Chlorpromazine (CPZ) is an antipsychotic agent of the aliphatic phenothiazine group, and it is also useful as an antinauseant and for treating hiccups. It was first developed and used to treat mental illnesses in Paris in 1951. The US FDA approved its use in 1954 and it is available in multiple dosage forms including oral tablets, syrup and injection in various strengths.

10. The mechanism of action of CPZ is multi-fold:[3]

    a. It blocks the effects of a neurotransmitter called dopamine in the central nervous system (CNS) leading to its antipsychotic effects
    b. It also possesses strong blocking effects on other parts of the nervous system producing sedation, muscle relaxation, and cardiovascular effects such as hypotension, tachycardia, and minor changes in electrocardiogram pattern.

11. The reported adverse effects of CPZ include, most commonly, centrally-mediated extrapyramidal symptoms (e.g. involuntary movements of the tongue, mouth, face, extremities etc), hypotension, sedation, and anticholinergic effects such as dry mouth, urinary retention, constipation etc. [3]

12. PK characteristics of CPZ:

    a. PK characteristics of CPZ show a high degree of variability. This is usually thought to be due to its extensive liver metabolising effect when the drug first passes through the liver after absorption (liver first pass effect).[4]
    b. Oral absorption is rapid but large variation in bioavailability (the rate and extent of a drug that actually reaches the circulatory system of the human body), peak plasma concentration (the maximum drug plasma concentration after absorption), and onset of action (the time required for the drug to reach the minimum effective plasma concentration to produce action) has been reported.[3]

b. For bioavailability, it has been reported to be dose-dependent and varies between 4-38% of the original dose.[4]
c. The half-life t½ (the period of time required for the amount or concentration of a drug to decrease by one half) of CPZ also demonstrates a large range of variation from 7.5 – 35 hrs.[5] For simplicity, however, the t½ of CPZ is usually taken as 30hr.[6]
d. CPZ is extensively distributed into body tissues and fluids. Its excretion is partly through kidneys and partly by biliary tract and faeces.

13. From the documents in relation to the present inquest I was provided; I noted that the deceased was prescribed, among other medications, with chlorpromazine (Largactil) 50mg three times a day and at night-time by Dr Noom Sai-hsam of the Psychological Unit of Lai Chi Kok Reception Centre Hospital on 16.11.2001. Nonetheless, there was no record of administering the drug during the stay at Lai Chi Kok.

14. From the report of Dr. Lee Wai-kit of Government Laboratory dated 7 January 2002, I noted a CPZ blood level of **9.7μg/ml** was detected in the deceased's blood which was delivered to the Laboratory on 23 Nov 2001.

15. From the autopsy report prepared by Dr Lam Wai-man Joey of the Forensic Pathology Service of the Department of Health, it was stated that the lethal range of CPZ is in the range of **3 –12 μg/ml**, hence the CPZ blood level of the deceased was well within the lethal range. Initially, it would therefore be logical to assume that the cause of death of the deceased was due to an overdose of CPZ.

16. However, according to the record of the Siu Lam Psychiatric Centre (SLPC), the deceased was only given a total of 5 doses of CPZ 50mg orally during his detention in SLPC. The time of administration was: 1600 and 1900 hours on 17.11.2001, and 1200, 1630 and 1900 hours on 18.11.2001. A graph describing the time of drug administration is shown in Figure (2).

17. In the report of Mr Leung Kam-shing of SLPC dated 18 March 2003, it was reported that there was a drastic decrease in body weight of the deceased from 84kg on 14.11.2001 to 65kg at autopsy on 22.11.2001.

18. This drastic drop in weight could partly be the result of a heavy loss of fluid due to osmotic diuresis from the deceased's uncontrolled diabetes. Consequently, this shrink in blood volume would artificially increase the concentration of the various substances in the blood.

19. Given this background, I believe some calculations utilizing the principles of PK should be able to provide some useful information as to whether the death of Cheung Chi-kin could be related to an overdose of CPZ.

20. In the process of performing the calculations, I have consulted 2 of my colleagues in the School of Pharmacy CUHK, namely, Prof Joan Zuo PhD and Dr Ophelia Yin PhD, who have extensive experience in calculations of this sort to help me with the technical part of this report. Prof Vivian Lee, another colleague in the School who is

an extremely experienced teacher in Clinical Pharmacy, has kindly tendered her assistance in information searching.

21. To help calculating, we have used Figures (2) and (3) to build the models for calculation and data were plugged into the concerned equations. Although there was some indication that the function of the 2 major organs for excretion of CPZ and methadone and their metabolites i.e. kidneys and liver, was somewhat compromised as a result of the deceased's long history of uncontrolled diabetes (Dr Lam's statement in court) and slight elevation of liver enzymes (Reference letter of Dr Lo Man-wai of Queen Elizabeth Hospital to corona dated 01.02.2002), we have assumed the function of the 2 organs to be close to normal as slight abnormalities at this level should have minimum effect on our final results.

22. For Figure (2), several assumptions were made to facilitate the subsequent calculation work:

    a. To facilitate our calculation, the time period between the 3 doses on 18.11.2003 was taken as 4 hours although the actual periods varied between 2.5 to 4.5 hours.
    b. The blood sample for post-mortem blood level determination was taken at 0700 hours on 19.11.2001. This would be an appropriate time as the body metabolic activities stop altogether after death.
    c. The PK characteristics after oral and intramuscular administration were assumed to be similar enough to be analysed by the same PK model.

23. The post-mortem blood concentration of CPZ on 19.11.2002 is C_F which represents the combined effect of the 2 doses of CPZ taken on 17.11.2001 (C_1) and the 3 doses taken on 18.11.2001.

24. In our calculation, we have taken two approaches in order to provide a more comprehensive and, hopefully, more reliable conclusion. Firstly, we have worked on the problem according to the natural time sequence i.e. a prospective approach starting from the time when the first of the 5 doses of CPZ 50mg was taken. Next, we have worked retrospectively based on the post-mortem blood level of 9.7μg/ml of CPZ with a view to find out what the original dose could be. For the 2 approaches we have taken, we have also analysed our data according to 2 possible scenarios: single dose vs multiple doses.

25. The detailed calculation work on CPZ is shown in Annex B. To summarize the results:

    a. Prospective multiple doses:
       C_F = 34.56 ng/ml
    b. Retrospective multiple doses:
       Number of doses (n) = mathematically not possible, which means by giving multiple doses of CPZ 50mg, it would not be possible to achieve the concentration of 9.7μg/ml.

d. Prospective single dose assuming CPZ was given 40 hours before the deceased's death:
$C_F = 23.69$ng/ml

d. Retrospective single dose:
Initial single dose given 40 hours before death = 102.4g (102,400mg) i.e. 2,048 tablets of CPZ 50mg or 2,048 ampoules of CPZ 25mg/ml x 2ml injection.

If it was assumed that the initial single dose was given shortly, say 14 hrs, before death,
Initial single dose = 56.3g (56,300mg) i.e. 1,126 tablets of CPZ 50mg or 1,126 ampoules of CPZ injection.

Methadone

26. Methadone is a synthetic narcotic analgesic. The principal therapeutic uses are analgesia and detoxification or temporary maintenance in narcotic addiction.

27. Major adverse effects of methadone include respiratory depression, circulatory depression, light-headedness, dizziness, sedation, nausea, vomiting, sweating etc. In view of the potential depressing effects on the central nervous system (CNS), it is recommended to be given with caution and in reduced dosage in patients who are concurrently receiving other medications that could also cause CNS depression, otherwise profound sedation or coma may result. [7]

28. PK characteristics of methadone:

a. $t_{½} = 48$hr [8]
b. Bioavailability = 0.75 [9]
e. Lethal range of plasma level = 0.4 –1.8 μg/ml [10]

29. From the information provided to me, I understand that the deceased was given two intramuscular doses of methadone 10mg in Queen Elizabeth Hospital within the period from 0100 to 0800 hours on 17.11.2001. Before this, he was also given several doses of methadone ranging from 40mg to 50mg daily from the period of 12.11.2001 to 14.11.2001. A graph describing the time of drug administration is shown in Figure (3).

30. Assumptions were also made for Figure (3) to facilitate our calculations:

a. The 3 oral doses of methadone were assumed to have been given in the morning of 12.11.2001 to 14.11.2001 at roughly the same time.
b. The average dose for these 3 doses was assumed to be 50mg as it was not specified in the record.
c. The PK characteristics of oral and intramuscular administration of methadone are similar enough to be analysed by the same model.
c. Post-mortem blood level determination was performed at 0700 hours on 19.11.2001.

31. The detailed calculation work on methadone is shown in Annex C. To summarize the results:
    a. Prospective multiple doses
       C_F = 118.37 ng/ml (=0.118μg/ml)
    b. Retrospective multiple doses
       Number of doses = mathematically not possible
    c. If concentration determination was performed at around 0900 on 17.11.2001, concentration = 0.197μg/ml

Discussion on Results Obtained

Chlorpromazine

32. The calculated concentration of CPZ at around 0700 on 19.11.2001 was 34.56ng/ml (0.03456μg/ml), hence substantially below the lethal range of 3 –12 μg/ml and thus the 5 doses of CPZ should not be directly related to death.

33. Of the 4 results obtained, given the background record of administration of CPZ in SLPC, only results (a) and (b) from paragraph (25) should be somewhat related to the truth. However, result (a) which should be the situation most closely resembling the truth is obviously not consistent with the laboratory findings and result (b) is self-explanatory. Even if it was assumed that CPZ was given as a single dose, result (c) is still not consistent with the laboratory findings. Results from (d) are obviously physically and physiologically impossible. Even if we assumed the bioavailability after intramuscular injection to be 2 times that of oral (which in reality is highly unlikely), the number of ampoules given 40 hours and 14 hours before death would be 1,024 and 563 respectively which is still physically and physiologically impossible.

34. Given the above, the possibilities which caused a plasma CPZ concentration of 9.7μg/ml could be:

    a. Mr Leung Kam-shing of SLPC has hypothesized that this could be due to a cellular breakdown of adipose tissues (lipolysis) caused by uncontrolled diabetes which released the CPZ that was originally stored there. While the process may be possible and the literature backup provided by Mr Leung is relevant and adequate, it must be pointed out that this should only remain theoretical and the probability of occurrence should best be supported by experimental evidence as to whether lipolysis induced by uncontrolled diabetes would actually produce post-mortem plasma concentrations of this level.

    b. A haemo-concentration effect arising from the loss of fluid due to uncontrolled diabetes leading to a shrink in blood volume, hence pushing up the blood concentrations of the substances.

    c. The occurrence of a post-mortem redistribution of drug from storage tissue where the concentration was high to areas of lower concentration e.g. blood.

    d. A combined effect of any or all of the above.

Methadone

35. The calculated concentrations of methadone at 0700 on 19.11.2001 and around 0900 on 17.11.2001 was 0.118μg/ml and 0.197μg/ml respectively, hence both fall below the lethal range of 0.4 –1.8μg/ml and thus the 5 doses of methadone should not be directly related to death.

36. According to the Government Laboratory result dated 7.1.2002, the toxicological analysis of the deceased's blood showed that the methadone level in blood was 0.88μg/ml which is within the lethal range. However, this elevated post-mortem plasma level of methadone is unreasonable as no further record of methadone administration was reported.

37. In the absence of any solid evidence, the most reasonable explanation is that concentration of drug in post-mortem blood specimens, even though taken from peripheral sites, will often be much higher than the perimortem plasma drug concentration particularly if several days have elapsed between death and post-mortem examination due to a post-mortem redistribution as mentioned in paragraph 34 (c). On top of this, other possibilities as for the case of CPZ certainly also exist. It is therefore difficult to compare the reported post-mortem blood concentration of a drug with literature values.[11]

Overall

38. From our calculations, it appears that the individual effects of CPZ and methadone should have minimal contribution to the death of the deceased as neither of the drugs was taken in high enough doses to cause death. Nonetheless, it remains possible and probable that the concurrent administration of the 2 drugs would result in enhanced side effect which would most likely be increased CNS depression leading to profound sleepiness and confusion. Under this enhanced effect, the victim would be less ready to respond, both mentally and physically, when a crisis occurs.

39. In addition, I would also like to address the other issues raised in the letter dated 11 June 2003 :

    a. (1) and (2) have been addressed by the above discussion.
    b. CPZ possesses strong anticholinergic as well as alpha-adrenergic receptor blocking effects.[3] The former effect normally causes mydriasis whereas the latter causes miosis. Nonetheless, in an acute overdose of CPZ, miosis would appear to predominate.[12, 13]
    c. The normal time required for ethyl alcohol to appear in the urine after consumption/injection is highly variable mainly depending on the amount of the chemical actually consumed/injected. In general terms, it takes approximately 1 hour to absorb from the gut into the blood. The blood concentration will then decrease with time and it takes about 2 hours after absorption to eliminate a 12oz beer.[13]

Summary and conclusion

40. We have performed the calculations in relation to the administration of CPZ and methadone by building a PK model to assimilate the real situations.

41. Our analysis does not support any direct relationship between the dosages of the drugs administered and the eventual death of the deceased.

42. Although the post-mortem blood levels of the drugs were within their reported lethal ranges, the possibility of lipolysis caused by uncontrolled diabetes exists but to establish this fact would require supporting evidence from experimental studies. Other possibilities including haemo-concentration effect and post-mortem redistribution also exist.

43. The combined effect of the 2 drugs when they were taken together could be additive to the potential life-threatening risk of uncontrolled diabetes.

References

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(Kenneth KC Lee)

23 June 2003
(date)

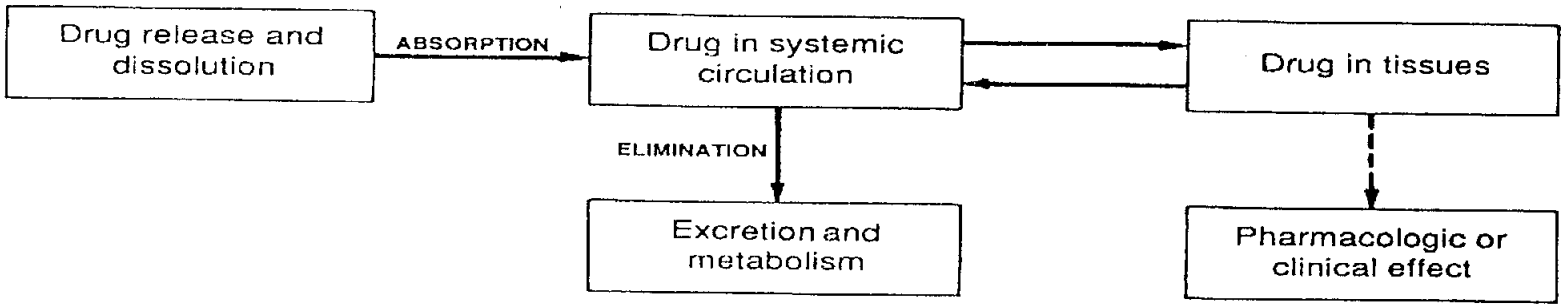

Figure 1. Relationship between the drug, its original product and the pharmacologic effect[1]

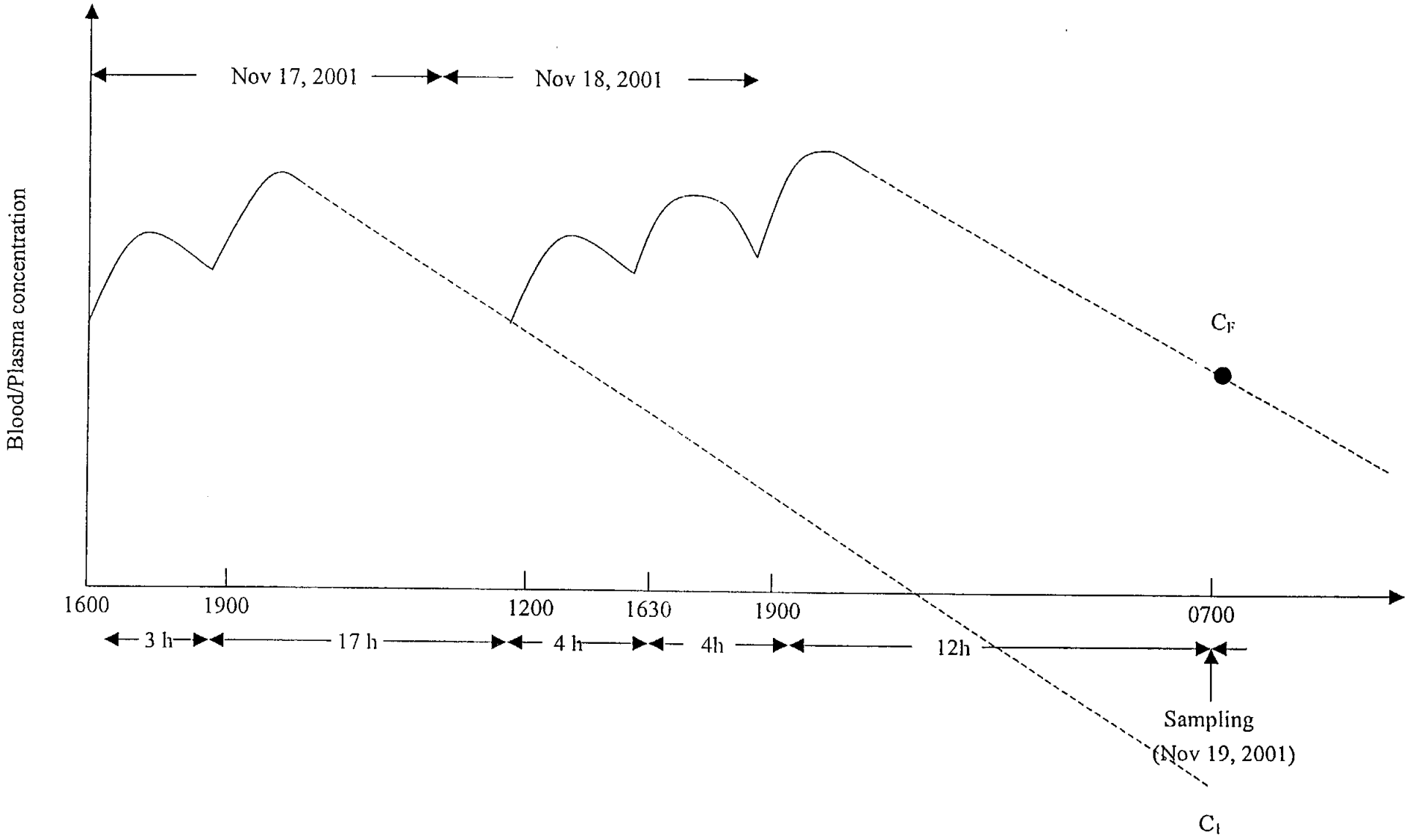

Figure 2 : Administration of Chlorpromazine

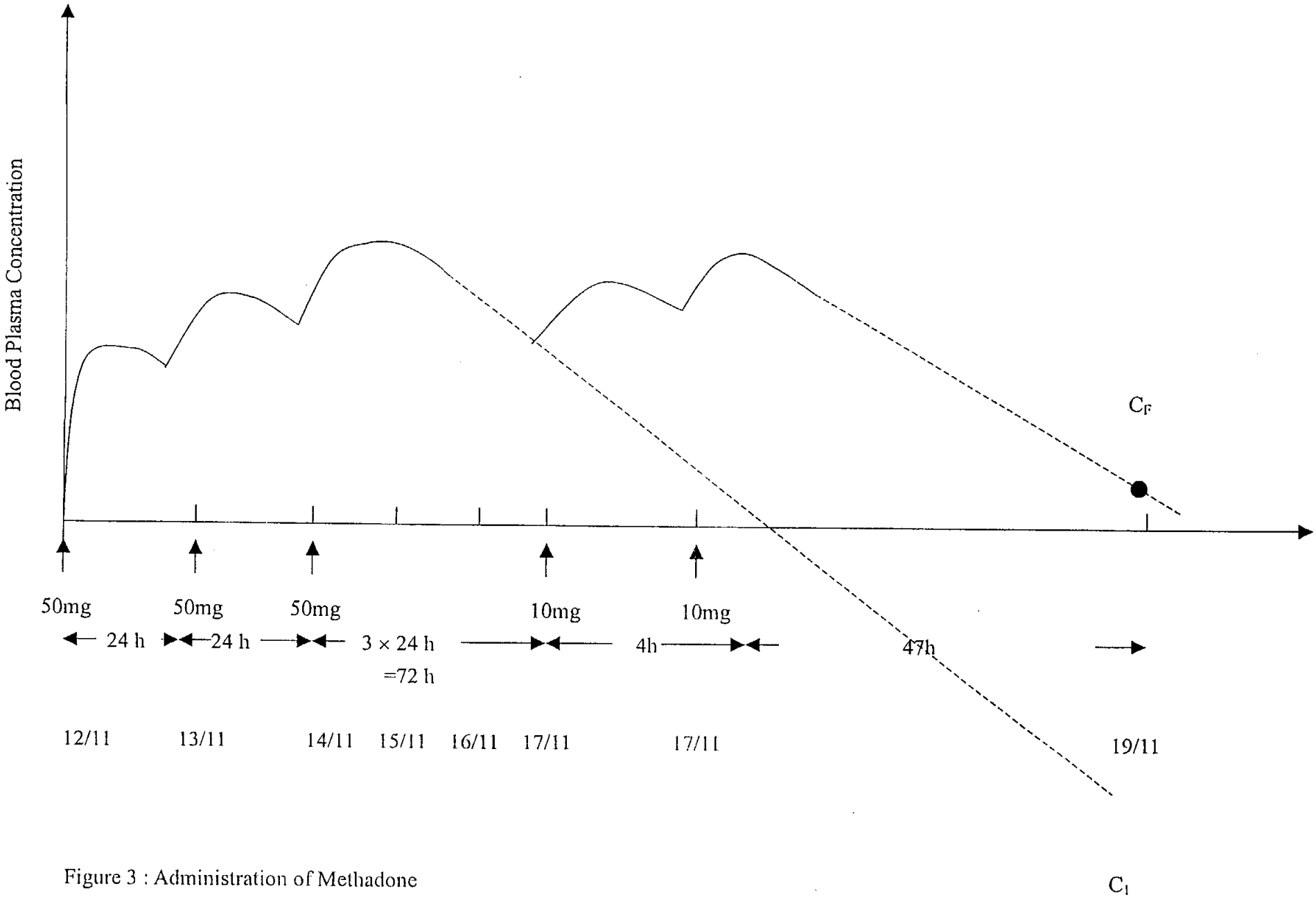

Figure 3 : Administration of Methadone

Annex A

CURRICULUM VITAE

KENNETH KWING CHIN LEE
B.Sc.(Pharm) MPhil PhD Reg. Pharm

PERSONAL DATA

NAME IN ENGLISH:	LEE KWING CHIN, KENNETH
HKID NUMBER :	[redacted]
NATIONALITY :	[redacted]
CURRENT EMPLOYMENT:	Professor and Head of Division Division of Pharmacy Practice School of Pharmacy Faculty of Medicine The Chinese University of Hong Kong
TELEPHONE NUMBER :	[redacted]
FAX NUMBER :	[redacted]
Email :	[redacted]

EDUCATION

Institution	Degree/Professional Qualification	Date
[redacted]	[redacted]	
University of Washington	BS(Pharmacy)	
Washington State Board of Pharmacy	Pass in State Board	
Pharmacy & Poisons Board of Hong Kong	Registered Pharmacist	
The Chinese University of HK	M.Phil	
The Chinese University of HK	Ph.D	

ACADEMIC AWARDS

University of Washington School of Pharmacy Dean's List — 75-76, 76-77

OVERSEAS ACADEMIC APPOINTMENT

Honorary Senior Lecturer, School of Pharmacy, University of London, U.K. — Jan 03 – Dec 04

AREA OF MAJOR RESEARCH INTEREST

Pharmacoeconomics and outcomes research

INTERNATIONAL APPOINTMENTS IN RELATION TO AREA OF RESEARCH INTEREST

Chair, Asia-Pacific Council, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) — 9/02

Member, Programme Committee, Asia-Pacific Meeting of ISPOR, Kobe, Japan Sept/2003 — 10/02

EXTERNAL EXAMINERSHIP

1. Higher Diploma in Pharmaceutical Technology, Hong Kong Institute of Vocational Education (Chai Wan) — 10/95-to date
2. Member of Internal Examining Committees, Dept of Economics CUHK — Dec 01

INVITED SPEAKER

1. "An update on Diabetes Mellitus" to pharmaceutical — 9/92

	staff of the Department of Health		
2.	"Cholesterol - its goods and bads" to members of the Repulse Bay Club sponsored by Bristol-Myers-Squibb	2/95	
3.	"Syndrome-X : a triad of Hypertension, Dyslipidaemia and Diabetes Mellitus" to members of the Society of Hospital Pharmacists of HK sponsored by Eli Lilly	6/95	
4.	Public lecture on "An update on diabetes care" sponsored by Vita Green Health Products Ltd.	7/96	
5.	"Health problems related to Hyperlipidaemia" to paramedical staff of Baptist Hospital	8/97	
6.	"The Metabolic Syndrome" to the Pharmacy Technicians Association of HK	12/97	
7.	"Diabetes and its related metabolic disorders" to the pharmaceutical staff of Baptist Hospital	7/98	
8.	"An Update on Diabetes Mellitus", 10th National Congress on Medical Economics, Shenzhen		11/98
9.	"An overview of Pharmacoeconomics" to students of Guangdong College of Pharmacy		11/99
10.	"Pharmacoeconomics : its importance and applications" to members of the HK Association of the Pharmaceutical Industry		2/00
11.	"Pharmacoeconomics : its relevance to hospital pharmacy practitioners" to pharmaceutical staff of Baptist Hospital		4/00
12.	"Methods of Pharmacoeconomic Research" at the Investigator Support Initiative Workshop sponsored by Pharmacia		6/00
13.	"Pharmacoeconomics : An Added Value to Pharmacy Practitioners", HK Pharmacy Conference		10/00
14.	"An Overview of Pharmacoeconomics", the Macau Pharmacists Association Annual Meeting		3/01
15.	"Pharmacoeconomic Research in Hong Kong", Faculty of Pharmacy Comenius University, Slovakia		5/01
16.	"Understanding your anti-rheumatic agents" to MSD patient group		12/01
17.	Chairman, Symposium on "Emerging issues in the management of acid-related disorders", Hong Kong		1/02
18.	Invited speaker "Seminar for Doctors to Help Beat Drugs", HK Medical Association		1/02
19.	Invited speaker "Overview of Pharmacoeconomics", City University of HK		4/02
20.	Invited speaker "Proper use of vitamins" by Vitagreen Health Products Co.		4/02
21.	Invited panellist, ISPOR 7th Annual International Meeting, Arlington, U.S.A.		5/02
22.	Invited speaker on pharmacology of proton pump inhibitors, British Medical Association, Hong Kong Branch		5/02
23.	Invited speaker, Pfizer Pharmacoeconomics and Outcomes Workshop		5/02
24.	Invited speaker, "Science of a new analgesic formulation", symposium by GSK		6/02
25.	Invited speaker, Pharmacoeconomics Workshp, Indonesian Ministry of Health		9/02
26.	Invited speaker, "Pharmacology of commonly abused substances", Continued Education courses for psychiatric nurses, HK Hospital Authority		11/02
27.	Invited speaker, public lecture on "Drugs for Allergy", organised by Schering Plough		12/02
28.	Invited speaker, "Clinical uses of vitamins" at Chinese Medical Association Meeting		4/03
29.	Invited speaker, "Treatment of dengue fever" at CE seminar of HK Medical Association		5/03

SERVICES TO UNIVERSITY

1.	Report on the review of CUHK University Health Service Dispensary service	9/99
2.	Member, CUHK Delegation to universities in Beijing and Nanjing	11/93
3.	Departmental Co-ordinator, United College	9/93-7/00
4.	Lecturer of General Education courses, United College	9/93- to date
5.	Supervisor of Senior Seminar G041, United College	9/93-7/00
6.	Term paper marker for Course 1411, United College	9/93 – to date
7.	Member, Board of Dept of Anatomy	9/00 – to date
8.	Member, CUHK Health Week Organizing Committee	5/02 – to date
9.	Member, CUHK Centre of Addiction Research and Education	5/02 – to date

SERVICES TO SOCIETY

1.	Expert Member, Investigation Committee on the Incident of Wrongly Dispensed Medicine at Cheung Sha Wan JC Clinic	12/97
2.	Expert Member, Expert Committee on Regulation of Health Claims	12/02

SERVICES TO GOVERNMENT COMMITTEES

1.	Chief Examiner in Pharmacy Practice, Examination Committee, Pharmacy & Poisons Board of HK	12/92-to date
2.	Member, Action Committee Against Narcotics (ACAN)	1/2003 – 12/2004
3.	Member, Pharmacy & Poisons Board of HK	1/91-12/93, 94-5
4.	Member, Poisons Committee, Pharmacy & Poisons Board	1/91-12/93
5.	Member, Treatment and Research Subcommittee, ACAN	1/99-to date
6.	Member, Working Group on Review of Methadone Treatment Programme, ACAN	5/99-to date
7.	Member, Steering Committee for the Drug Information Resource Centre, ACAN	9/99-to date
8.	Member, Fund Raising Committee for the Drug Information Resource Centre, ACAN	9/99-6/00
9.	Member, Task Force on Psychotropic Substance Abuse, ACAN	4/00-to date
10.	Chairman, Monitoring Committee on Naltrexone therapy, ACAN	5/02-to date
11.	Member, Chinese Medicines Board, The Chinese Medicine Council	9/02-8/05
12.	Member, Expert Committee on Regulation of Health Claims	12/02-to date

SERVICES TO ACADEMIC INSTITUTIONS IN MAINLAND CHINA

1.	Regular guest lecturer to Guangdong College of Pharmacy, Guangzhou	
2.	Organiser and Chairman, Pharmacy CE seminars for the Chinese Pharmaceutical Society (Guangdong branch)	3/96
3.	Hong Kong Co-ordinator and invited speaker, 10th National Congress on Medical Economics, State Drug Administration of China, Shenzhen	11/98
4.	Member, Organising Committee of the Joint Meeting with the Beijing Pharmacology Society, Hong Kong Pharmacology Society	3/99
5.	Expert Member, Institute of Health Economics Research, State Drug Administration of China	2/99-to date

CONTRIBUTIONS TO THE PHARMACY PROFESSION

1.	President, The Practising Pharmacists Association of HK	87-88 88-89 89-90
2.	President, The Pharmaceutical Society of HK	89-93 94-95

3.	Editor, The Journal of Practising Pharmacists of HK	85-89
4.	Member, Organising Committee of Exhibition on 'Gastrointestinal Drugs and You'	12/85
5.	Member, Organising Committee of Exhibition on 'Labelling of Dispensed Medicines'	11/89
6.	Chairman, Ad Hoc Committee for the campaign of Pharmacy course	88-90
7.	Supervisor and Advisor, exhibition on "Pharmacists and Public Health" organised by the student Pharmacy Society of CUHK	8/96
8.	Convenor, Working Group on CE programmes for practising pharmacists of HK	10/98-3/99
3.	Vice-Chairman and CUHK liaison person, Pharmacy Central Continuing Education Committee	3/00-1/01

ADVISORSHIPS

1.	Advisor of Pharmacy Practice, Drug and Poisons Information Bureau, CUHK	1/90-to date
2.	Advisor to Pharmacy Student Society, CUHK	10/92-to date
3.	Working Party on Pharmacy Course, CUHK	5/90-8/92
4.	Departmental Advisory Group, Dept. of Applied Science, Hong Kong Technical College	4/91-8/93
5.	Recruitment Board, Dept. of Applied Science, Hong Kong Technical College	9/92-3/95

INTERNATIONAL AWARDS FOR RESEARCH

Best Podium Presentation Award for the paper "Cost-effectiveness analysis of high dose IV omeprazole infusion as adjuvant therapy to endoscopic haemostasis for bleeding peptic ulcers" by KKC Lee et al at the International Society for Pharmacoeconomics and Outcomes Research 2nd Annual European Conference, Edinburgh, Nov 99

Best Contributed Paper Award for the paper "A pharmacoeconomic analysis of weight-reduction therapy in a hypothetical cohort of obese Chinese patients with impaired glucose tolerance" by KKC Lee et al at the International Society for Pharmacoeconomics and Outcomes Research 6th Annual International Meeting, Arlington, Virginia USA, May 2001

EDITOR/REVIEWER FOR INTERNATIONAL PUBLICATIONS

1. Reviewer, *Value in Health*
2. Reviewer, *Journal of Medical Economics*
3. Member, International Editorial Board, *Textbook for Pharmaceutical Technology*
4. Paper reviewer, International Society for Pharmacoeconomics and Outcomes Research annual international and European meetings
5. Member, Editorial Board, *Disease Management*
6. Advisor, Regional Editorial Board, MIMS Hong Kong

PUBLICATIONS

THESES

1. Lee KKC, Pharmaceutical Studies of Epirubicin Emulsion, MPhil thesis, May 91
2. Lee KKC, The Measurement of Insulin Resistance in the Assessment of Drug Effects in Patients with the Metabolic Syndrome, PhD thesis, Nov 98

PEER-REVIEWED JOURNALS

1. Lee K, Chan K. Pharmacokinetics of epirubicin emulsion and solution in rabbits after intrahepato and intravenous injection. Methods and Findings 1992;14(8):655-9
2. Lee K, Chan K, Leung WT, Leung NWY, Ho S, Chan M, Lau CC, Tao M, Lau WY & Shiu W.

Disposition of epirubicin in oily contrast medium after intravenous and intrahepato-arterial administration in liver cancer : A preliminary report. Euro J Drug Meta Pharmacok 1992;17(3):221-6

3. Lee K, Chan K. Biopharmaceutical studies of a formulated epirubicin emulsion. Pharmaceutical Science Communications 1993;4(1):39-44
4. Young RP, Critchley JAJH, Lau M, Lee KKC , Chan TYK, Anderson DC. Reliability of glucose measurement using the HemoCue Analyser in hypoglycaemia. Ann Clin Biochem 1994;31:573-5
5. Lee KKC, Chan TYK, Raymond K, Critchley JAJH. Pharmacist attitudes to adverse drug reaction reporting in Hong Kong. Ann Pharmacotherapy 1994;28(12):1400-3
6. Chan TYK, Lee KKC, Chan AYW, Critchley JAJH. Poisoning due to Chinese proprietary medicines. Hum Exp Toxicol 1995;14:434-6
7. Lau GSN, Lee KKC, Luk CT. Self-Medication among University Students in Hong Kong. Asia Pac J Public Health 1995; 8(3):153-7
8. Young RP, Critchley JAJH, Anderson PJ, Lau SW, Lee KKC Chan JC. The Short Insulin Tolerance Test using venous sampling, Diabet Med 1996;13:423-33
9. Lee KKC, Chan A, Lau G, Chan TYK, Critchley JAJH. Use of Benzodiazepines in Hong Kong in 1990-93 : The impact of regulatory actions. J Clin Toxicol 1995;33(6):597-602
10. Chan TYK, Leung CY, Ng David, Lee KKC. Inadequate warnings and misleading information in the package inserts of over-the-counter medicated oils containing methyl salicylate in Hong Kong, Ann Pharmacotherapy 1995;29:1301-2
11. Chan TYK, Lee KKC, Chan AYW, JAJH Critchley : Utilization of Antidiabetic Drugs in Hong Kong : relation to the common occurrence of antidiabetic drug-induced hypoglycaemia amongst acute medical admissions and the relative prevalence of NIDDM. Int J Clin Pharmacol Ther 1996;34(1):43-6
12. Chan TYK, Lee KKC, Critchley JAJH. Drug information requirements of practising pharmacists in Hong Kong. J Clin Pharm Ther 1996;21:325-330
13. Lee KKC, Chan TYK, Lee CW. Improvements are needed in the existing packaging of medicated oils containing methyl salicylate. J Clin Pharm Ther1997;22(4):279-282
14. Anderson PJ, Chan JCN, ChanYL, Tomlinson B, Young RP, Lee Z, Lee KKC, Metreweli C, Cockram C, Critchley JAJH. Visceral fat and cardiovascular risk factors in Chinese NIDDM patients. Diabetes Care 1997;20(12):1854-1858
15. Lau JYW, Sung JJY, Lee KKC, Yung MY, Wong SKH, Wu JCY, Chan FKL, Ng EKW, You JHS, Lee CW, Chan ACW, Chung SSC. A comparison of high-dose omeprazole infusion to placebo after endoscopic hemostasis to bleeding peptic ulcer. New Engl J Med 2000, 343(5) :310-316
16. You JHS, Lee KKC, Ho SSS, Sung JJY, Kung NNS, Yung MY, Lee CW, Yee GC. Economic analysis of four triple regimens for the treatment of helicobacter pylori-related peptic ulcer disease in inpatient and outpatient settings in Hong Kong. Alimen Pharmacol Ther 2001;15:1009-1015
17. Tang E, Lai C, Lee KKC, Wong SM, Cheng G, Chan TYK. Relationship between patients' knowledge and anticoagulation control. Ann Pharmacother 2003;37:34-9
18. Lee KKC, You JHS, Ho SSS, Leung WYS, Thomas GN, Chan JCN, Tomlinson B, Critchley JAJH. A pharmacoeconomic analysis of weight-reduction in a cohort of obese Chinese patients with impaired glucose tolerance utilizing data from a non-Chinese ethnic group (submitted to PharmacoEconomics for publication)
19. Lee KKC, You JHS, Wong ICK, Kwong SKS, Lau JYW, Chan TYK, Lau JTF, Leung WYS, Sung JJY, Chung SSC. Cost-effectiveness analysis of high dose IV omeprazole infusion as adjuvant therapy to endoscopic treatment of bleeding peptic ulcer. Gastrointest Endosc 2003;57(2):160-4
20. Chan TYK, Lee KKC. Pharmacoeconomics and healthcare decision-making – an Asian perspective. PharmacoEconomics (in press)
21. You JHS, Lee KKC, Chan FKL, Chan TYK, Lau WH. Cost analysis of celecoxib and conventional NSAIDS with or without gastroprotective agents for treatment of osteoarthritis and rheumatoid arthritis in Hong Kong. Alimen Pharmacol Therap 2002;16:2089-96
22. You JHS, Lee KKC, Sung JJY, Lau WH, Lee IYC, Yung MY, Chung SSC, Chan FKL. Eradication of helicobacter pylori to prevent peptic ulcers prior to NSAID drug therapy in a Chinese population – A cost-effectiveness analysis (Submitted to Aliment Pharmacol Therap)
23. You JHS, Lee VWY, Au P, Critchley JAJC, Lee KKC. Evaluation of antimicrobial use in patients with community acquired pneumonia in a Hong Kong teaching hospital, Am J Health-syst Pharm 2002;59:1785-6

24. Chan FKL, Hung LCT, Suen BY, Wu JCY, Lee KKC, Leung VKS, Hui AJ, To KF, Leung WK, Wong VWS, Chung SC, Sung JJY. A double-blind, randomised comparison of celecoxib versus diclofenac plus omeprazole in preventing recurrent ulcer bleeding in arthritis patients. N Engl J Med 2002;347:2104-010

25. Lee KKC, You JHS, Ho JTS, Suen BY, Yung MY, Lau WH, Lee VWY, Sung JJY, Chan FKL. Economic analysis of celecoxib versus diclofenac plus omeprazole for the treatment of arthritis in patients at risk for ulcer disease.. Alimen Pharmacol Therap (in press)

OTHER PUBLISHED ARTICLES

Lee K & Ng KW : A step towards Unit-Dose dispensing (The Medication System at Tsuen Wan Adventist Hospital), The Journal of Practising Pharmacists 1986; 4(1) :27-31

BOOK CHAPTERS

Lee KKC, Pharmacology of MDMA, ketamine and methamphetamine (Ice), Common Poly-Substance Abuse Resource Book for seminar for doctors to help beat drugs 2002, p24-26, Hong Kong Medical Association

ABSTRACTS PRESENTED IN INTERNATIONAL/REGIONAL MEETINGS

1. Chan K, Lee K, Tao M, Leung WT, Ho S & Shiu W : Epirubicin disposition after administration via the hepatic artery of a Lipiodol-drug mixture in patients with liver cancer, J. Pharm Pharmacol Abs. Br. Pharm Conf. Aug 91
2. Lee K & Chan K : Acute LD-50 of an emulsion drug-carrier system for Epirubicin in rabbits and mice, Proceedings of Sixth S.E. Asia/Western Pacific Regional Meeting of Pharmacologists July 1991
3. Lee KKC, Chan TYK, Raymond K and Critchley JAJH : Pharmacist attitudes to adverse drug reaction reporting in Hong Kong, 10th International Conference on Pharmacoepidemiology Aug 1994 Stockholm, Sweden
4. Young RP, Critchley JAJH, Lau M, Anderson PJ, Lee KKC and Chan JCN : Variation in dose responses during Insulin Sensitivity Testing in healthy subjects, 15th International Diabetes Federation Congress Kobe 1994, Nov 94 Kobe Japan
5. Lee KKC, Chan A, Lau G, Chan TYK and Critchley JAJH: Use of Benzodiazepines in Hong Kong in 1990-93 : The Impact of Regulatory Actions, 5th WFACTC Taipei 94
6. Lee KKC, Chan TYK, Lau G and Critchley JAJH : Toxic potential of three commonly used medicated oils in Hong Kong, 5th WFACTC Taipei 94
7. Tomlinson B, Critchley JAJH, Sanderson JE, Chan TYK and Lee KKC : Thiazide Diuretic Dose-Response in Chinese Hypertensives, 10th International Interdisciplinary Conference on Hypertension in Blacks, St. Tomas, US Virgin Islands, USA Jun 95
8. Tomlinson B, Mak TWL, Shek CC, Lee KKC, Say JTK, Lam CWK, Critchley JAJH and Masarei JRL : Dose-Response Study of Gemfibrozil in Chinese Patients with Combined Hyperlipidaemia, 11th Asian-Pacific Congress of Cardiology, Aug 95
9. Tomlinson B, Mak TWL, Shek CC, Lee KKC, Say JTK, Lam CWK, Critchley JAJH and Masarei JRL : Effects of Gemfibrozil 900 Mg Tablet Once Daily in Chinese Patients with Dyslipidaemia, 11th Asian-Pacific Congress of Cardiology, Aug 95
10. B Tomlinson, JAJH Critchley, JE Sanderson, TYK Chan, KKC Lee and KS Woo : Vasodilating effect of hydrochlorothiazide in young Chinese hypertensives, The First Pacific Rim Hypertension Conference, Tokyo Oct 95
11. Lee KKC, Tomlinson B, Say TK, Critchley JAJH, Mak TWL and Lam CWK : Effect of Bezafibrate on Dyslipidaemia and Insulin Sensitivity in Chinese Patients, 7th SEA-WP RMP, Manila, Philippines, Nov 95
12. Lee KKC, B Tomlinson, YL Chan, PJ Anderson, RP Young, JAJH Critchley & C Metreweli. Relationships between measurements of obesity, insulin sensitivity and plasma lipids in Chinese patients with dyslipidaemia treated with bezafibrate, Asian-Pacific Congress on Vascular Disease Prevention, Singapore March 96
13. B Tomlinson, KKC Lee, TK Say, JAJH Critchley, TWL Mak & CWK Lam. Reduction of coronary heart disease risk factors with bezafibrate treatment in dyslipidaemia, 6th Int Congress of Cardiovascular Pharmacotherapy, Sydney Feb 96
14. B Tomlinson, KKC Lee, PJ Anderson, SK Lee, JCN Chan, CS Cockram & JAJH Critchley. Relationships between responses to short insulin tolerance test and oral glucose tolerance test in insulin resistant

dyslipidaemic patients. 3rd International Diabetes Federation Western Pacific Regional Congress, Hong Kong Sept 96

15. KKC Lee, B Tomlinson, YL Chan, PJ Anderson, JCN Chan, JAJH Critchley, C Metreweli. Inter-Relationships of different indices of obesity in patients with dyslipidaemia and insulin resistance. 3rd International Diabetes Federation Western Pacific Regional Congress, Hong Kong Sept 96
16. Lau JYW, Sung JJY, Lee KKC, Yung MY, Wu JCY, Wong SKH,Ng EKW, Chan FKL, Chan ACW, Chung SSC. Intravenous omeprazole infusion after endoscopic ulcer hemostasis : A double blind, placebo-controlled randomised trial. Digestive Week, May 99
17. Lee KKC, You JH, Lau JYW, Sung JJY, Yung MY, Suk-San Ho S, Lee CW, Chung S. Cost-effectiveness anaylsis of high dose IV omeprazole infusion as adjuvant therapy to endoscopic haemostasis for bleeding peptic ulcers. International Society for Pharmacoeconomics and Outcomes Research Second Annual European Conference. Value in Health. 1999;2(5):366. Edinburgh, Nov 99
18. You JH, Lee KKC, Ho SSS, Sung JJY, Yung MY, Lee CW, Yee GCY. Cost-minimization analysis of two triple regimens for the treatment of Helicobacter pylori-related peptic ulcer disease. International Society for Pharmacoeconomics and Outcomes Research Second Annual European Conference. Value in Health. 1999;2(5):378. Edinburgh, Nov 99
19. Lee KKC, You JHS, Ho SSS, Chan TYK. A pharmacoeconomic model to assess the cost-effectiveness of trovafloxacin compared to ceftazitime for nosocomial pneumonia in a public hospital setting in Hong Kong. Presented at the 5th Annual International Meeting of ISPOR, Washington D.C. May 2000.
20. You JHS, Lee KKC, Chan FKL, Sung JJY, Yung MY, Chung SSC. Eradication of Helicobacter pylori to prevent peptic ulcers prior to NSAID therapy – a cost-effectiveness analysis. The 3rd Annual European Conference of ISPOR, Belgium Nov 2000
21. Lee KKC, Tam KY, Leung SM, You JHS, Chan TYK. Cost of illness on patients in a public hospital with severe exacerbation of COAD. 3rd Annual European Conference of ISPOR, Belgium Nov 2000
22. Lee KKC, You JHS, Ho SSS, Leung WYS, Thomas GN, Chan TYK, Critchley JAJH. A pharmacoeconomic analysis of weight-reduction therapy in a hypothetical cohort of obese Chinese patients with impaired glucose tolerance. ISPOR 6th Annual International Meeting, Washington DC May 2001-09-22
23. Lee KKC, Chan TYK, Lau JTF, Kwong SKS, Lee WSY. A study on the health effects of flu and flu-like illnesses in the working population and their cost impact to a big corporation in Hong Kong. 4th Annual European Conference of ISPOR, France Nov 2001
24. You JHS, Lee KKC, Ho SSS, Sanderson J, Sung JJY. Cost-effectiveness analysis of a chest pain unit – a restructured approach in risk stratification of chest pain. 4th Annual Annual European Conference of ISPOR, France Nov 2001
25. You JHS, Lee KKC, Chan FKL, Ho SSS, Chan TYK. Cost analysis of celecoxib and conventional NSAIDS with or without gastroprotective agents for treatment of osteoarthritis and rheumatoid arthritis. 4th Annual European Conference of ISPOR, France Nov 2001
26. Zhang JX, Lau EMC, Lee KKC. Cost-effectiveness of pharmacotherapy of osteoporosis in Chinese women in Hong Kong. ISPOR 7th Annual International Meeting, Washington DC, May 2002
27. Lee KKC, Tang P, Chan S, Liu P, Cheung KW, Leung KS. Incidence and economic burden of deep vein thrombosis after total hip replacement in Hong Kong. Annual European Conference of ISPOR, Rotterdam, Nov2002
28. You JH, Ho J, Lau W, Lee VW, Chan FK, Lee KKC. A cost analysis of celecoxib versus diclofenac plus omeprazole for the treatment of arthritis in a group of high-risk Chinese patients. ISPOR Eighth Annual International Meeting, Washington DC, May 2003
29. Lee VW, Chan WK, Lam NL, Lee KKC. Evaluation on the cost of management of acute myocardial infarction in a local public hospital in Hong Kong. ISPOR Eighth Annual International Meeting, Washington DC, May 2003
30. Lee KKC, Piovella F, Turpie A, Planes A, Wang C, Lee W, Houshan L, Lee L, Perdriset G, Rouillon A, Nguyen T, Gallus A. Assessment of the incidence of DVT in Asia following major orthopaedic surgery (The AIDA Study): Cost of management in 6 Asian countries – An interim analysis. ISPOR First Asia-Pacific Conference, Kobe, Japan Sept 2003
31. Lee KKC, Lee VW, Kwong KS, Wong I, Kung N, Leung WT, Chan H, Chan FK, Sung JJY. Cost of management of hepatitis B and its complications in Hong Kong Chinese. ISPOR First Asia-Pacific Conference, Kobe, Japan Sept 2003

32. Piovella F, Turpie AG, Wang CJ, Lee WC, Lee KKC, Lee LH, Lu H, Planes A, Perdriset G, Rouillon A. AIDA – Assessment of the incidence of deep vein thrombosis in Asia following major orthopaedic surgery – Interim data. 6th EFFORT Congress, Helsinki, June 2003

ABSTRACTS PRESENTED IN LOCAL MEETINGS

1. Lee K : Future direction of patient counselling in Hong Kong, Proceedings of the Society of Hospital Pharmacist of HK, Annual Conference Nov 1992
2. Young BP, Lee KKC, Anderson PJ, Lau MSW, Tomlinson B, Chan JCN and Critchley JAJH : Insulin Sensitivity Testing : An assessment of alterations in insulin resistance in response to drug therapy. Proceedings of the 9th Annual Science Meeting of the Soc. for the Study of Endo, Metab & Reprod. Publication No. 9, Abs. P25, Hong Kong 1994 Nov
3. Lee KKC, Tomlinson B, Critchley JAJH, Say TK, Mak TWL and Lam CWK : Effects of Lowering Plasma Triglycerides on Insulin Sensitivity in Patients with Dyslipidaemia, Annual Conference Society for the Study of Endocrinology, Metabolism and Reproduction, Hong Kong Oct 95
4. CML Chen, KKY Wan, MHM Ling and KKC Lee : Cytotoxic reconstitution services in Hong Kong, Present and Future, Annual Conference of the Society of Hospital Pharmacists of Hong Kong, Oct 95

ONGOING RESEARCH PROJECTS

1. The effect of orlistat and rosiglitazone on insulin action in a group of Chinese patients affected by the metabolic syndrome – a randomised, single-blinded, and placebo-controlled study
   Investigators : Lee KKC, You JHS, Tomlinson B, Chan JCN, Critchley JAJH
2. An open trial of Vitacalm in the management of primary insomnia
   Investigators : Wing YK, Lee TS, Cheung A, Lee KKC
3. A study on the health effects of flu and flu-like illness in the working population and its cost impact to a big corporaion in Hong Kong
   Investigators : Lee KKC, Chan TYK, Kwong SKS, Lau JTF
4. Effect of COX-2 specific inhibitor on recurrence of ulcer haemorrhage in high-risk patients : a double-blind comparison with co-therapy of PPI with conventional NSAID
   Investigators : Chan FKL, Sung JJY, Lee KKC
5. Hepatitis B multinational medical resource use and cost survey
   Investigators : Lee KKC, Kwong SKS, Chan TYK, Lau JTF, Wong ICK, Sung JJY
   Project Co-ordinator for the Asian Pacific region
6. Cost analysis study of gemcitabine chemotherapies
   Investigators : Lee KKC, Kwong SKS, Mok TSK
7. Cost of illness of Type 2 diabetes
   Investigators : Lee KKC, Ng YC, Kwong SKS, Lau JTF, Chan TYK
8. Cost of management of deep vein thrombosis
   Investigators : Lee KKC, Kwong SKS, Chan TYK, Lau JTF

COMPETITIVE GRANTS RECEIVED

1. RGC Earmarked Grant, Sept 99 HK 765,000 (CUHK4315/99M)
   Co-investigator "Does acid suppression reduce rebleeding in peptic ulcers after endoscopic haemostasis – a double blind, placebo-controlled randomised trial"
2. RGC Earmarked Grant, Sept 2000 HK811,200 (CUHK4069/00M)
   Principal investigator "The effect of orlistat and rosiglitazone on insulin action in a group of Chinese patients affected by the metabolic syndrome – a randomised, single-blinded and placebo-controlled study"
3. Industrial Support Fund Grant, Jan/99 HK 3.23 million
   Co-investigator "Establishment of a certified Drug Evaluation Unit for assessing the quality of oral generic drugs in HK"
   Source : Industrial Support Fund 1/99
   Amount : 3.23 million
4. Medicine Panel Direct Grant, Dec 93 HK40,000
   Principal investigator "Insulin sensitivity testing in healthy subjects"

5. Medicine Panel Direct Grant, Nov 94 HK36,000
Co-investigator "Insulin sensitivity testing in dyslipidaemic patients"

Calculations on Chlorpromazine

$$C_p = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

1. Prospective Multiple Doses

$\tau_1 = 3h$ $\quad n = 2$ $\quad t = 17h+20 = 37hr$ $\quad V_D = 1365(L)$

$$C_1 = \frac{0.32 \times 1.65 \times 50}{1365 \times (0.023-1.65)} \times (-)\frac{0.1289}{0.0667} \times 0.427$$

$$= 0.009809\ \mu g/mL\ (mg/L)$$

$\tau_2 = 4h$ $\quad n = 3$ $\quad t = 12h$ $\quad V_D = 1365(L)$

$$C_F = 0.009809 + (-)\frac{0.32 \times 1.65 \times 50}{1365 \times (0.023-1.65)} \times (-)\frac{0.2412}{0.0879} \times 0.7588$$

$$= 0.009809 + 0.02475$$

$$= 0.03456\ mg/L\ (\mu g/mL) = 34.56\ ng/mL$$

$$C_p = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

2. Retrospective Multiple Doses

$F = 0.32$ $ka = 1.65h^{-1}$ $Do = 50$ mg $V_D = 1365(L)$ $k = 0.023h^{-1}$
$\tau = 4h$ $t = 12hr$

$$C_F = 9.7\ \mu g/mL\ (mg/L) = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

$$9.7 = \frac{0.32 \times 1.65 \times 50}{1365 \times (0.023-1.65)} \times (-) \frac{1-e^{-0.092n}}{0.0879} \times 0.7588$$

$$9.7 = 0.1026 \times (1-e^{-0.092n})$$

$$(-)\ 93.53 = e^{-0.092 \times n}$$

$$n = \text{impossible}$$

$$C_p = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

3. Prospective Single Dose

$ka = 1.65h^{-1}$ (average of $1.8h^{-1} \sim 1.5h^{-1}$)

$t½\lambda$ (elimination half life) = 30hr

$k = \frac{0.693}{30} = 0.023h^{-1}$

$V_D = 21$ L/kg = 1365(L)

$F = 0.32$

Do = 250mg

$$C_F = \frac{F \times ka \times Do}{V_D\,(ka-k)} \left(e^{-kt} - e^{-kat} \right)$$

$$C_F = \frac{0.32 \times 1.65 \times 250}{1365 \times (0.023-1.65)} \times \left(e^{-0.023 \times 40} - e^{-1.65 \times 40}\right)$$

$$= 0.05944 \times 0.3985$$

$$= 0.02369 \text{ mg/L } (\mu g/mL) = 23.69 \text{ ng/mL}$$

$$C_p = \frac{F \times ka \times Do}{V_D (k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

4. Retrospective Single Dose

a. If Cp = 9.7 µg/mL (mg/L) at 40hr

$$9.7 = \frac{0.32 \times 1.65 \times Do}{1365 \times 1.627} \times (e^{-0.023 \times 40} - e^{-1.65 \times 40})$$

$$Do = 102383.42 \text{ (mg)} = 102.38 \text{ (g)}$$

b. If Cp = 9.7 µg/mL (mg/L) at 14hr

$$9.7 = \frac{0.32 \times 1.65 \times Do}{1365 \times 1.627} \times (e^{-0.023 \times 14} - e^{-1.65 \times 14})$$

$$Do = 56298.88 \text{ (mg)} = 56.30 \text{ (g)}$$

Calculations on Methadone

$$C_p = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

1. Prospective Multiple Doses

$F = 0.75$ $ka = 0.39h^{-1}$ $k = 0.0144h^{-1}$ $V_D = 123(L)$

$(n1 = 3$ $\tau 1 = 24h$ $t1 = 174h$ $D1 = 50mg)$

$$C_1 = \frac{0.75 \times 0.39 \times 50}{123 \times (0.0144-0.39)} \left[\left(\frac{1-e^{-3x0.39x24}}{1-e^{-0.39x24}} \right) e^{-0.39x174} - \left(\frac{1-e^{-3x0.0144x24}}{1-e^{-0.0144x24}} \right) e^{-0.0144x174} \right]$$

$$= (-)\frac{14.63}{123 \times 0.3756} \times (-)\frac{0.6454}{0.2922} \times 0.0816$$

$= 0.0571$ mg/L (μg/mL) $= 57.1$ ng/mL

$(n2 = 2$ $\tau 2 = 7h$ $t2 = 47h$ $D2 = 10mg)$

$$C_F = C_1 + \frac{0.75 \times 0.39 \times 10}{123 \times (0.0144-0.39)} \left[\left(\frac{1-e^{-2x0.39x7}}{1-e^{-0.39x7}} \right) e^{-0.39x47} - \left(\frac{1-e^{-2x0.0144x7}}{1-e^{-0.0144x7}} \right) e^{-0.0144x47} \right]$$

$$= 0.0571 + (-)\frac{2.925}{123 \times 0.3756} \times (-)\frac{0.1826}{0.09589} \times 0.5082$$

$= 0.11837$ mg/L (μg/mL) $= 118.37$ ng/mL

$$C_p = \frac{F \times ka \times Do}{V_D\,(k-ka)} \left[\left(\frac{1-e^{-nka\tau}}{1-e^{-ka\tau}} \right) e^{-kat} - \left(\frac{1-e^{-nk\tau}}{1-e^{-k\tau}} \right) e^{-kt} \right]$$

2. Concentration at 0900 on 17.11.2001

$\tau_1 = 24h$ $\quad t1 = 3x24+72+8 = 152h$ $\quad D1 = 50mg$

$$C_1 = \frac{0.75 \times 0.39 \times 50}{123 \times (0.0144-0.39)} \left[\left(\frac{1-e^{-3x0.39x24}}{1-e^{-0.39x24}} \right) e^{-0.39x152} - \left(\frac{1-e^{-3x0.0144x24}}{1-e^{-0.0144x24}} \right) e^{-0.0144x152} \right]$$

$$= (-) \frac{14.63}{123 \times 0.3756} \times (-) \frac{0.6454}{0.2922} \times 0.1121$$

$$= 0.07841 \text{ mg/L } (\mu g/mL) = 78.41 \text{ ng/mL}$$

$t2 = 1h$ $\quad \tau = 7h$ $\quad D2 = 10mg$

$$C_F = C_1 + \frac{0.75 \times 0.39 \times 10}{123 \times (0.0144-0.39)} \times (-) \frac{1-e^{-2x0.0144x7}}{1-e^{-0.0144x7}} \times e^{-0.0144x1}$$

$$= 0.07841 + (-) \frac{2.925}{123 \times 0.3756} \times (-) \frac{0.1826}{0.0959} \times 0.985$$

$$= 0.07841 + 0.1188 = 0.19753 \text{ mg/L } (\mu g/mL) = 197.53 \text{ ng/mL}$$