討論文件
二〇〇三年七月十八日

立法會保安事務委員會及衞生事務委員會
二〇〇三年七月十八日聯席會議

有關囚犯張志堅於二〇〇一年十一月十九日於小欖精神病治療中心死亡事件

目的

在二〇〇三年三月五日召開的立法會保安事務委員會及衞生事務委員會會議(聯席會議)上，小欖精神病治療中心監督就二〇〇一年十一月十九日小欖精神病治療中心一名囚犯死亡的事件提出推論。本文件旨在就此提供醫學專家的意見，並載列政府對個案的回應及擬議的未來工作路向。

推論

2. 在二〇〇三年三月五日舉行的聯席會議上，小欖精神病治療中心監督根據他本人翻查醫學文獻所得及死因研訊的舉證，提出一項推論，從中或可解釋何以死者血液含有大量氯丙嗪以及身上有不尋常的針孔。扼要重述，監督推測由於死者長期患有糖尿病，他可能因為糖尿病情未受控制，引致脂肪組織細胞分解[即脂肪分解(lipolysis)]，因而釋放出大量原來儲存於脂肪的氯丙嗪。

醫學專家意見

3. 我們邀請了三位獨立醫學專家 – 香港大學內科講座教授及內分泌科主任林小玲教授、香港大學臨床藥劑科副教授張文勇醫生及中文大學藥劑學院教授和藥劑執業學部主管李炯前教授探討推論能否成立，以及研究可能與死者死因有關的醫學問題。有關的專家意見(中譯本)分別載於附件 A、B 及 C。

4. 專家意見的要點如下：

林小玲教授

- 死者自幼長期患有糖尿病。

- 死者死前數天的確出現嚴重血糖過多和糖尿性酮酸中毒(屬糖尿病不受控制的一種急性情況，必須緊急治療)的症狀。

- 這些嚴重的新陳代謝失調，在未經診斷及未獲治療的情況下可導致死亡。

- 根據Gormsen et al (Forensic Sci Int, 1985) 就二十四個死於糖尿昏迷個案所作出的報告，所有死者的血糖水平皆高於 19.44mmol/L。本個案的死者的血糖含量達45.7mmol/L，較前述報告中死於糖尿昏迷的死者血糖含量平均值43.1mmol/L更高。對比起來，其他並非死於糖尿昏迷的死者，其血糖含量通常很低，許多時候甚至接近零。

- 酮性糖尿病昏迷可能是死者致死的原因。

- 糖尿性酮酸中毒時，脂肪分解會明顯增多，理論上可釋出先前積聚在脂肪組織中可溶於脂肪的藥物，如氯丙嗪。不過，我們無法斷定這高含量的氯丙嗪是如何及何時在死者體內組織積聚。

- 不排除還有其他致死的可能原因，例如氯丙嗪中毒。

<u>張文勇醫生</u>

- 氯丙嗪可溶於脂肪。

- 理論上脂肪分解的確有可能釋放出大量氯丙嗪，令血液中的氯丙嗪含量升高。這有可能促成死者死亡。

- 脂肪分解和屍體釋化現象，可能會大大增加死者血液的氯丙嗪含量。

- 死者右肩的三個針孔及相關瘀痕可能是試圖在右頭靜脈插輸液導管所造成。三個針孔位於右頭靜脈之上。這並非靜脈輸液最常用的位置，不過，如果不能經由外圍靜脈較多的前臂或肘部注射，也可採用這個位置。

<u>李炯前教授</u>

- 根據記錄，死者死前被羈押前後均曾服用氯丙嗪和美沙酮，但死者服用兩種藥物的劑量都不足以致命，所以由口

服氯丙嗪和美沙酮而引致的個別效應，對死者致死的原因影響極為輕微。

- 以追溯方式計算，死者死前14小時或須一次過注射約1 126安瓿的氯丙嗪(每安瓿份量為50毫克)，死後血液的氯丙嗪濃度才會達到9.7μg/ml；但是，無論在用藥或生理上都並不可能做到這個劑量的注射。

- 死者死後血液含有高濃度的氯丙嗪，原因可能是：

  - 推論所指的脂肪分解，但這只屬理論，最好還是有實驗證據支持。

  - 因糖尿病不受控制導致體液流失，從而引起血液濃縮效應，令體內血量減低。

  - 由於死後屍體釋化現象，藥物從濃度較高的儲存組織流向濃度較低的地方(如血液)。

  - 以上多項的綜合效應。

5. 有見及此，我們亦邀請了衞生署法醫科主任顧問醫生蒙海強醫生[1]覆核原先的驗屍結果[2]及死者體液樣本分析。蒙醫生提出的專業意見主要如下：

- 按照世界衞生組織發出的國際疾病統計分類的定義(及規定)，驗屍報告把氯丙嗪、美沙酮及乙醇的不良作用列為原因 I (即直接導致死亡的情況)，以及把糖尿病列為原因 II (即致死的其它主要情況，但與第 I 死因無關)並無不妥。因此，目前驗屍報告所述的醫學死因無須作任何更改。

- 至於氯丙嗪的來源，蒙醫生會接受推論所指，即由脂肪分解所釋出，而非來自注射或服食等外在源頭。

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1 蒙醫生是名列於香港醫務委員會專科醫生名冊(法醫病理學)內的註冊醫生，具備以下專業資格：香港大學內外全科醫學士、臨牀法醫學文憑(LAS)、法醫病理學文憑(LAS)、香港病理學專科學院院士及香港醫學專科學院院士(病理學)。

2 驗屍報告所述的死因為“氯丙嗪、美沙酮及乙醇之不良作用”，而“糖尿病”則被列為“致死的其他主要情況，但與致死的疾病或情況無關”。

- 至於死者血液中美沙酮的含量方面，蒙醫生留意到死者因糖尿病酮酸中毒而脫水，以致體內出現血液濃縮的情況。他也會接受乙醇可能是在囚犯死後才產生的，因為唯有這樣才能解釋為何只在血液而非玻璃體液或尿液中發現乙醇。

- 死者身上的針孔應由大口徑的針頭造成，且可能是試圖插入靜脈輸液導管不遂的結果。驗屍時針孔滲血顯示針孔是在死前不久所引致，這與死者死前不久(即接近死亡時及不超過一或兩小時)曾經在屯門醫院進行復甦急救未果，並非不吻合。

<u>政府當局的觀察結果及回應</u>

6. 正如保安事務委員會上一份文件(CB(2)1323/02-03(01))第 15 至 18 段所解釋，死者在小欖精神病治療中心囚室的整段期間均受閉路電視監視。分區閉路電視系統保存了約 17 小時持續及完整的錄影帶，攝錄了事發前死者在囚室內的活動、被發現和急救的經過，以及事件完結後囚室內一段短時間的情況。在細看錄影帶後，並沒有發現任何不尋常的情況。警方可以確認，在大概 17 小時的錄影帶中，約有 14 小時是在發現死者和進行急救之前緊接攝錄的。此外，根據負責的救護員的口供，在運送死者由小欖精神病治療中心至屯門醫院時，並沒有發現死者膊頭附近有針孔，而根據有關的救護車行車記錄冊上亦沒有這項發現。這項事實已由其中一名救護員在死因研訊庭上宣誓作實。(然而，在屯門醫院負責對死者作復甦急救的醫生於死因研訊庭上亦供稱，他只曾於死者左手內踝位置進行靜脈注射。因此，並無確切証據可指出誰人有可能在死者身上造成有關針孔。)

7. 三名提供專業意見的醫學專家皆接納因脂肪分解而導致死者血液中出現高含量的氯丙嗪的情況，在理論上是可以成立的。雖然我們並沒有資料顯示這高含量的氯丙嗪是如何及何時在死者體內的組織積聚，不過，從死者過往羈押於懲教院所時的醫療記錄及期間所發生的一些事件的記錄，皆顯示出死者對氯丙嗪是有所認識的，甚至可能基於某些原因，倚賴該種藥物。在一九九九年十二月中，當死者於喜靈洲戒毒所服刑時，院方曾連續十九天處方及施用氯丙嗪於他身上。其中於一九九九年十二月十五日，他曾獲注射一安瓿的氯丙嗪(50 毫克/兩毫升)，以舒緩他的斷癮症狀。在一九九九年十二月二十九日，死者曾主動要求喜靈洲戒毒所的醫生增加氯丙嗪的劑量，說該藥物可醫治其失眠。

8. 總括以上各項(第四至七段)及各位醫學專家的意見，酮性糖尿病昏迷可能是死者的致死原因，惟其可能性有多高則難以追溯。根據專家意見，死者死後血液中高含量的氯丙嗪，極不可能是由外注射進體內，因為這在生理學上來說是不可能的。

9. 我們曾考慮是否應根據《死因裁判官條例》第 20(1)條向原訟法庭申請就有關個案進行另一次死因研訊[3]，或根據《調查委員會條例》第 2(1)條[4]委任委員會進行調查。我們基於法律、醫學及政策上各方面的考慮，否決有關的做法，考慮事項包括下列各點：

- 雖然新發現的證據或會有助進一步了解死者的死因，而且醫學專家的意見亦支持所提出的推論，但是仍缺乏結論性的証據証明死因及在死者死亡前實際上有沒有發生脂肪分解的現象。

- 就目前情況而言，驗屍報告提出的醫學死因看來仍然成立。在驗屍報告中，糖尿病已被列為致死的其他主要情況(請參閱蒙醫生的意見的第一點)。

- 在申請進行另一次死因研訊時，縱然有新的證據，我們仍需令原訟法庭信納是有需要或適宜進行另一次研訊。在這個個案中，新的專家意見是否可以對原來研訊的裁決(即"存疑裁決")作出重要的改變，仍是存疑的。如裁決的結果可能會與原來的一致，則法庭並不會信納有需要進行另一次研訊。

- 死者的死因已經過警方的詳細調查及死因裁判法庭的正式研訊，懲教署的研訊委員會及一個由兩名獨立的非官守太平紳士作為成員的特別工作小組，亦已就事件進行了深入的探討，以確定在制度上是否有不足之處，以及所需作出的改善。此外，事件亦曾多番在保安事務委員會及衞生事務委員會會議上詳細討論；我們亦已向獨立醫學專家取得了詳細的意見。雖然個案值得深究，但展開另一次死因研訊，或委任調查委員會進行研訊，看來並不能帶來新的得着，以更能符合公眾利益。

- 就死者家人而言，重新進行死因研訊或調查，可能會再次觸動他們已開始平復的創傷以及無端延長他們的傷痛。

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[3] "(1) 凡有適當利害關係的人或律政司司長在公開法庭上提出申請，而原訟法庭信納：
(a) 死因裁判官沒有進行應予進行的研訊；
(b) 死因裁判官已進行研訊，但由於欺詐、證據不被接納、法律程序失當(包括不遵從第 14(3)條)、查訊不足或其他原因，而有需要或適宜進行另一次研訊；或
(c) 死因裁判官已進行研訊，但由於有新事實的證據發現，而有需要或適宜進行另一次研訊，
則原訟法庭可命令就有關死亡個案進行研訊，倘若已進行研訊，則原訟法庭可推翻死因裁判官或陪審團在該研訊所作出的裁斷。"

[4] "(1) 行政長官會同行政會議可委任一名或多於一名委員(以下稱為委員會)，調查任何公共機構的經營或管理、任何公職人員的行為或其認為與公眾有重大關係的任何事宜。"

未來工作路向

10. 當局重申，我們將致力為犯人提供最佳的服務以保障犯人的安全及讓他們有機會重建新生。懲教署會繼續落實在二〇〇三年一月於委員會上承諾的改善措施，並將進度向保安事務委員會滙報。懲教署亦會進一步跟進改善犯人的羈押及醫療服務的安排。

保安局
二〇〇三年七月

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:
Direction des Expertises Judiciaires, Montréal, Québec, Canada.

Authors:
Péclet C; Picotte P; Jobin F

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%.

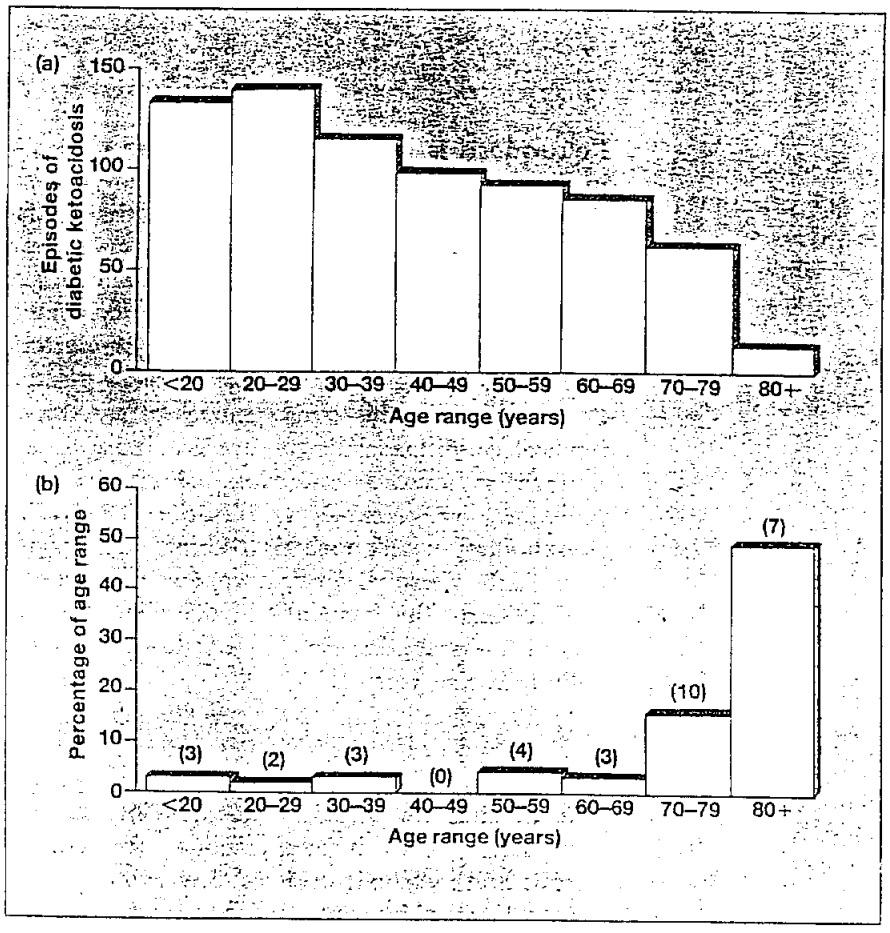


Fig. 49.1. (a) Age distribution of 746 episodes of diabetic ketoacidosis observed in Birmingham during the period 1971–85. (Paediatric cases are not represented in this series.) (b) Age distribution of deaths related to diabetic ketoacidosis (n = 32) occurring during these episodes. Numbers of deaths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

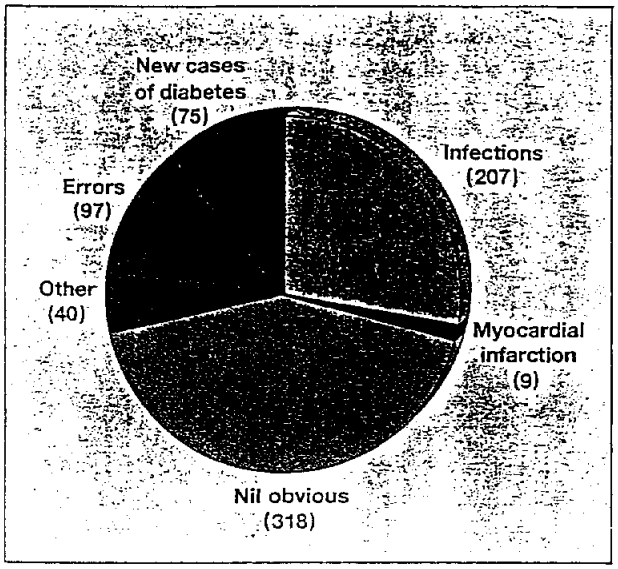


Fig. 49.2. Precipitating causes of 746 episodes of diabetic ketoacidosis observed in Birmingham during the period 1971–85.

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

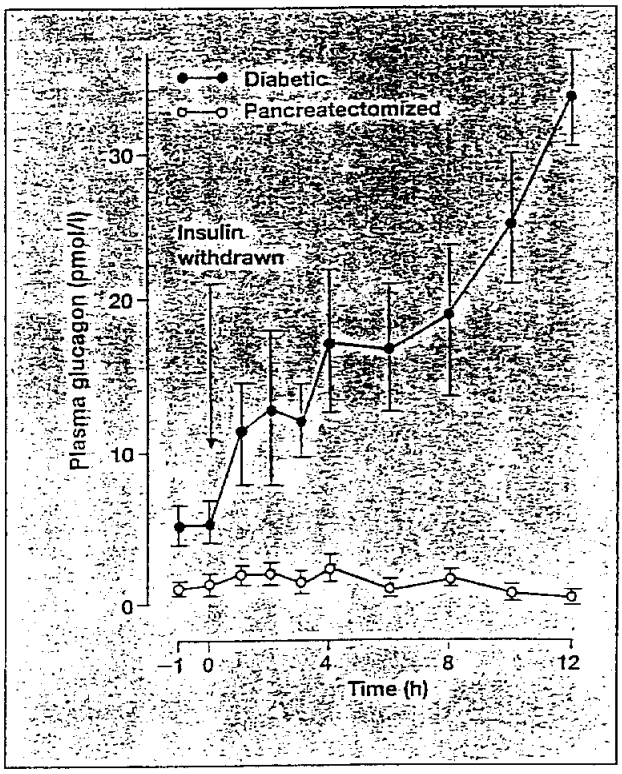


Fig. 49.3. Plasma concentrations (mean ± SEM) of glucagon in six IDDM patients and four pancreatectomized subjects after withdrawal of insulin. (Reproduced with permission from Barnes *et al.* 1977 [14].)

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

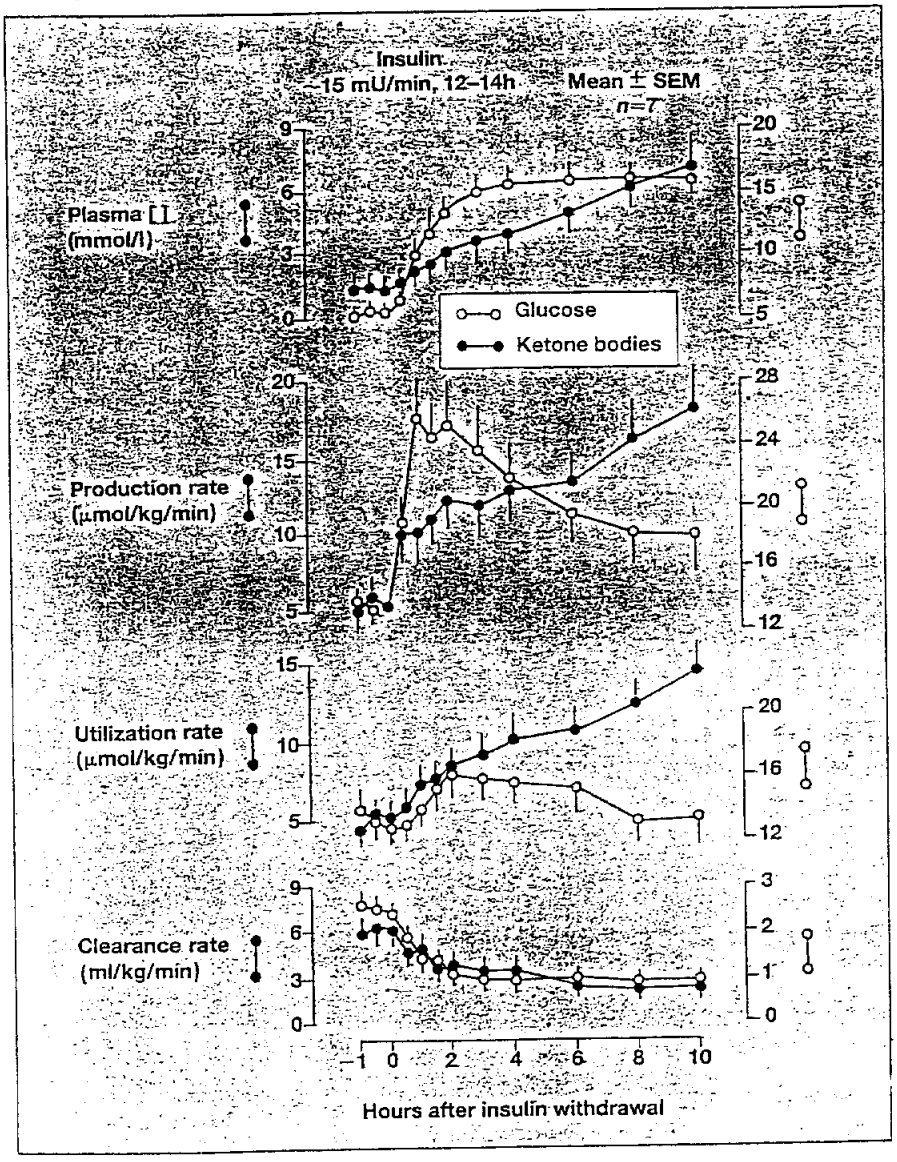


Fig. 49.4. Changes in plasma concentrations and in the rates of production, utilization and clearance of glucose and ketone bodies following withdrawal of insulin from seven IDDM patients. (Reproduced from Miles *et al.* 1980 [17] with permission of the authors and the American Diabetes Association Inc.)

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.

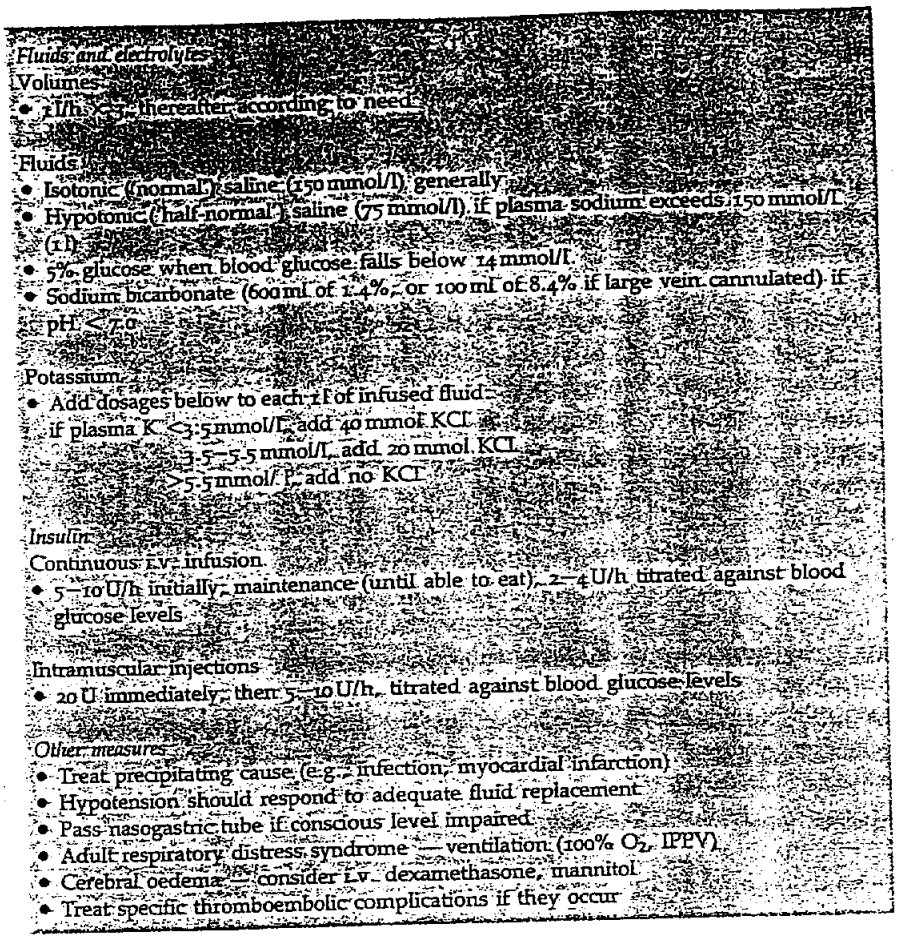
Rehydration is started with isotonic saline (150 mmol/l) containing appropriate potassium supplements (see below). Isotonic saline is used in preference to hypotonic saline (unless plasma osmolarity is significantly raised), to minimize the rapid movement of extracellular water into cells as blood glucose 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

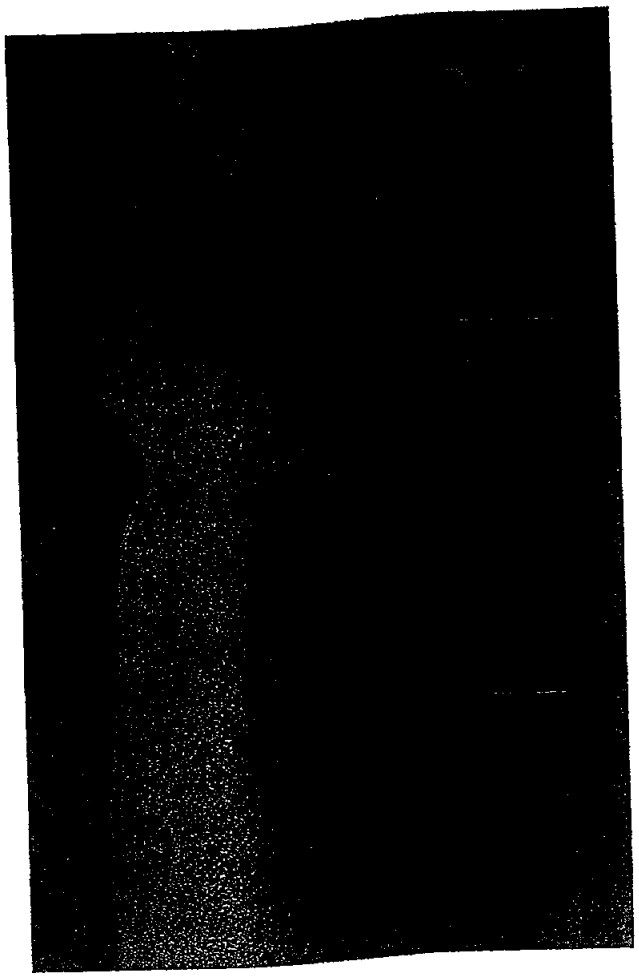


Fig. 49.5. Extensive necrosis of superficial tissues, which required skin grafting, following extravasation of 8.4% sodium bicarbonate solution.

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].

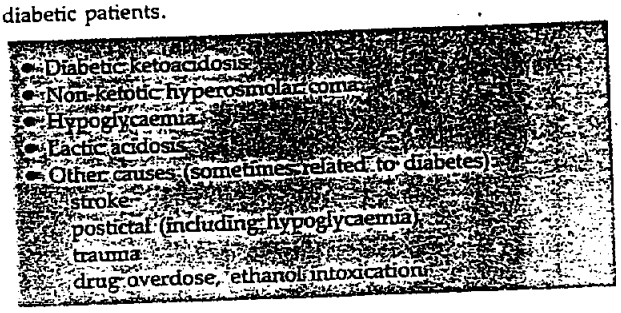
Sodium dichloroacetate has recently received attention as a potential adjunct in the management of lactic acidosis [93]. By stimulating the activity of pyruvate dehydrogenase, dichloroacetate lowers blood lactate levels in patients with lactic acidosis associated with a variety of conditions [94]. To 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.

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譯本 **附件B**

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彭女士：

有關囚犯張志堅的死因研訊CCDI-2139/2001

本人現應林小玲教授的要求，就你本年三月二十八日的來函附件B所載的問題提供進一步資料。本人將會專注回答有關臨床藥劑的問題，並只會就氯丙嗪所屬範疇發表意見。現就有關問題回應如下：

氯丙嗪可否在不會令死者出現任何明顯徵狀情況下於人體組織和脂肪內逐漸累積和存留?

氯丙嗪屬脂溶性物質，可存留於人體組織和脂肪。舉例來說，腦部的氯丙嗪濃度可高於血液中的濃度十倍。每個人對氯丙嗪的反應可差距甚大，而且未必會造成任何明顯影響。

假如血液中的氯丙嗪含量約爲每毫升9.7微克，一般人可否在此情況下存活?就一般人而言，該種藥物在血液中的含量要達至甚麼水平才致命?經驗出血液中含有該濃度藥物的死者是否有可能已適應該種藥物，因此即使血液中的氯丙嗪含量達至如此高水平，他仍可在小欖精神病治療中心生存40小時才死亡?

血液中倘每毫升含有大約9.7微克氯丙嗪，即已較一般治療水平超逾十倍，這肯定是屬於會使人中毒的範圍。這種情況雖然危險，但本人不敢猜說這是否一定致命。據文獻記載，曾有人服下10克氯丙嗪，但仍然存活。一般而言，氯丙嗪可說是一種較安全的藥物，因其具有較大的安全系數（即致命劑量是正常劑量的二百倍）。雖然血液中含大量氯丙嗪也未必能令人即時死亡，但對生命仍會構成威脅，例如可能會令血壓下降、壓仰呼吸、或引致抽搐，這些情況均需要提供維生治療。患者一旦獲得治理，康復的機會則甚爲樂觀。

雖然本人曾猜說即使血液中含有大量氯丙嗪，人也能夠存活下來，但若說在如此高含量的情況下人仍沒有中毒的跡象則不大可能。本人認爲，死者血液中一直含有如此大量氯丙嗪，以及死者已適應該種藥物的說法不大可能成立。

假如死者在送進小欖精神病治療中心前曾遭注射如此大量令其致死的氯丙嗪，他能否在該中心生存40小時?

假設每毫升血液含有9.7微克氯丙嗪便會致死，則死者在40小時後才引致死亡的可能性很低。藥物經吸收和帶送後，其在血液中的含量通常會隨時間而下降。就氯丙嗪而言，它會在肝臟經過代謝變化或分解，其代謝物便會經小便排出。因此，經過40小時後，體內的藥物含量一般預期會不斷減少。然而，即使體內的藥物總含量會慢慢減少，但脂解作用(lipolysis)或會釋出大量氯丙嗪，因而可能令血液中的氯丙嗪含量提高，最後可能導致死亡，這一點是有可能的。不過，這只是理論上有可能而已。

死者血液中的氯丙嗪含量積聚至每毫升9.7微克的水平，是否有可能是由於脂解作用（死者有酮類酸中毒(ketoacidosis)的現象，顯示死者可能有脂解作用的出現）和死後的脂肪分解(fat decomposition)現象，引致其體重在五天內劇降19公斤而導致的?

正如上文所述，這在理論上是可能的。另一方面，死者的體重下降19公斤，是十分值得注意的。就這宗個案而言，死者的體重下降會是分別因爲血糖過多(hyperglycemia)和脂解作用加速，引致出現滲透利尿(osmotic diuresis)的情況，結果

令體液和脂肪流失。

假如死者因氯丙嗪的有害作用致死，那死者應是在死前多久被施用氯丙嗪？

本人不能從一個單一的藥物水平讀數而回答上述問題，因爲這還需要考慮到死者的病歷，以及調查研訊的結果。

假如在不久前才施用氯丙嗪，究竟需要服下或注射多少氯丙嗪，才可以令血液中的氯丙嗪含量達至每毫升9.7微克這個水平？

這個問題並無固定答案。定期服用這種藥物的病人，其血液中的氯丙嗪含量爲每毫升30至350毫微克，但這並不一定表示死者曾被施用較正常高30至300倍的劑量。這種藥物的吸收和帶送情況，以及所發生的代謝變化，均會因人而異。再者，這種藥物確有可能因脂解作用和屍體釋化的現象而被釋出。

透過一連串假設，我們可以理論計算出劑量。爲方便計算，現以每毫升10微克(即每公升10毫克)這個單位作爲一個活人血液中的氯丙嗪含量，然後假設人體有20公升血液，即體內便有200毫克氯丙嗪，但並非全部氯丙嗪會被腸臟吸收。一般來說，被吸收的氯丙嗪只佔30%左右。此外，這種藥物在人體內會不斷分解和消減。因此，在理論上，氯丙嗪的劑量應會超過500毫克。

氯丙嗪可引致陰莖持續勃起症(priapism)的副作用嗎？有沒有配製的藥物含有能提高服用者性能力的吩噻嗪(phenothiazine)這種成分？這些藥物容易在藥房購買得到嗎？

據報氯丙嗪會引致陰莖持續勃起症，但這並非常見和可預計的副作用。較常見的影響是性官能障礙(sexual dysfunction)。時至今日，威而鋼(Viagra)是較有效幫助勃起的藥物。

有沒有藥物(註冊或非註冊藥物)在服用後，可令其在死後驗屍時，檢出血液中有氯丙嗪代謝物的含量？

根據臨床慣例，氯丙嗪並不屬其他吩噻嗪的代謝物。氯丙嗪本身經過代謝變化後會產生不少活躍及不活躍兩類代謝物。上述問題的答案在於採用的分析方法能有多精確地將氯丙嗪從其他物質中區別出來。至於是否有可能因其他具有類似化學特質的物質而引起誤測，則可由政府化驗師作出澄清。

按當時情況來看，我們是否可以說血糖過高及酮類酸中毒是導致死者死亡的原因；而經脂解作用和屍體釋化現象而導致死者血液中含有致命濃度的氯丙嗪是次要的原因？

糖尿性酮類酸中毒患者的情況會十分危險，如不被發現和得到治理，很可能會因而致死。另一方面，脂解作用和屍體變化亦會令死者死後血液中的氯丙嗪含量大大提高。

撇開屍體釋化能進一步令血液中氯丙嗪含量提高這一點，經脂解作用釋出的氯丙嗪所引發的有害作用，會否是導致死者死亡的主因？抑或酮類酸中毒引起的併發症和氯丙嗪的有害作用均有可能令張先生死亡？

經脂解作用釋出並進入血液循環系統的氯丙嗪亦可能是導致死者死亡的原因，或其中一個副因。

如對上述各點仍有問題，本人定樂意進一步解答。

（簽署）（Bernard Cheung）

二零零三年四月二十七日

[本文以英文版為準]

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黃福來先生

黃先生：

死因研訊 CCDI-2139/2001 —— 囚犯張志堅

謝謝送來死者驗屍照片，以供研究右肩的疑似針孔。

單憑照片作出推測，不免受到局限。我只能說，右肩三個針孔及相關瘀痕可能是試圖在右頭靜脈插輸液導管所造成。三個針孔位於右頭靜脈之上。右頭靜脈由右臂向上伸延，經三角肌與胸大肌之間的溝槽，然後深入身體，與右鎖骨之下的腋脈連接。這並非靜脈輸液最常用的位置。不過，如果不能經由外圍靜脈較多的前臂或肘部注射，也可採用這個位置。

如有需要，以上各點，我樂意進一步引申。

(簽署)
張文勇

二零零三年七月五日

副本送：林小玲教授

[本文以英文版為準]

譯 本

附件 C

死因研訊 CCDI-2139/2001

囚犯張志堅

1. 本人李炯前，現應政府保安局的要求，就上述法庭案件的死因研訊提供專業意見。本人知道，這些意見將提交立法會保安事務委員會和衞生事務委員會即將舉行的會議。如有需要，此事會作進一步處理，以便向原訟法庭申請重開死因研訊。

2. 本人現任香港中文大學藥劑學院教授和藥劑執業學部主管，亦是倫敦大學藥劑學院榮譽高級講師(其他資料請參閱附件 A 夾附的履歷表)。本人以前曾為十多宗法庭案件提供專業意見，該等案件涉及販毒檢控、吸毒者的死因調查和其他刑事罪行。

3. 在這份報告中，本人的主要責任是：

   a. 根據藥物代謝動力學的準則，解釋驗屍結果顯示死者血液中含過量氯丙嗪和美沙酮的情況；

   b. 根據(a)項的推論，提供獨立的專業意見，以探討死者的死因是否與上述的用藥有關。

4. 本人的報告分以下部分：

   a. 簡介藥物代謝動力學，以及氯丙嗪和美沙酮兩種藥物，特別是兩種藥物在藥物代謝動力學上的特性；

   b. 探討藥物代謝動力學的計算結果；

   c. 結論。

簡介

5. 藥物代謝動力學是一門衞生科學，主要研究一種藥物的物理化學特性與其藥理或臨牀效應之間的關係。圖表(1)概括描述這種動態關係。[1]

6. 評估一種藥物在體內的藥物代謝動力最直接的方法，是量度血液、血清或血漿中的藥物濃度。藥物的藥理效應和毒性通常與藥物在血液中的濃度有關。

7. 藥物在體內持續處於動態。為了解釋複雜的生物系統，我們通常對藥物的移動情況作簡單的假設，並建構多個數學模式，以模擬藥物的吸收、散布和排洩過程。這些數學模式有助發展若干方程式，以闡述體內藥物濃度隨時間的變化。

8. 藥物代謝動力學模式可應用於以下情況：[2]

   a. 在任何劑量療程中預計血漿的藥物濃度；

   b. 計算每名病人的最高劑量療程；

   c. 估計藥物可能的累積量；

   d. 找出藥物濃度與藥理效應或毒性之間的關係；

   e. 評估同一種藥物不同劑型之間的差別；

   f. 解釋身體的生理轉變如何影響藥物的吸收、散布和排洩；

   g. 解釋藥物之間的相互影響。

氯丙嗪

9. 氯丙嗪是脂肪吩噻嗪羣中的抗精神病藥物，對治療噁心和打嗝亦有功效。巴黎在一九五一年最先開發和使用氯丙嗪醫治精神病。美國的食物及藥物管理局在一九五四年批准使用該藥，該藥現時有具不同藥力的口服藥片、藥水和注射劑等。

10. 氯丙嗪有多方面的效用：[3]

   a. 氯丙嗪抑制一種名為多巴胺的神經傳感媒體在中樞神經系統中的效應，以達致抗精神病的效果；

   b. 氯丙嗪對於神經系統其他部分亦具有強大的抑制效力，從而鎮靜神經、鬆弛肌肉，以及產生心血管效應，例如低血壓、心搏過速和心電圖模式的細微變化。

11. 氯丙嗪最常見的報稱副作用包括中樞協調錐體外病徵(例如舌頭、口部、面部和四肢不由自主的動作)、低血壓、鎮靜神經和抗膽鹼效應，例如口乾、蓄尿和便秘等。[3]

12. 氯丙嗪的藥物代謝動力學特性如下：

a. 氯丙嗪的藥物代謝動力學特性變化不定。人們通常認為這是由於藥物被吸收後首次通過肝臟(肝臟首過效應)，造成廣泛的肝臟代謝效應所致。[4]

b. 藥物經口腔吸收的速度頗快，但據報在生物有效性(藥物實際傳送到人體循環系統的速率和幅度)、血漿最高濃度(藥物被吸收後在血漿中的最高濃度)和起始效應(藥物到達最低有效血漿濃度以產生效應所需的時間)三方面却有很大的變動幅度。[3]

c. 生物有效性據報取決於藥物的劑量，可以是原來劑量的 4% 至 38%不等。[4]

d. 氯丙嗪的半衰期 t½ (藥物劑量或濃度減少一半所需的時間)亦有很大的變動幅度，由 7.5 小時至 35 小時不等。[5]不過，為簡單起見，氯丙嗪的 t½通常當作 30 小時。[6]

e. 氯丙嗪遍散身體組織和體液，部分經腎臟排洩，部分經膽道和糞便排洩。

13. 從這次研訊提供的文件，我留意到除其他藥物外，死者曾得荔枝角收押所醫院的龍世山醫生在二零零一年十一月十六日開處氯丙嗪(Largactil)，日夜合服三次，每次 50 毫克。不過，死者在荔枝角收押所羈留期間並沒有服此藥的記錄。

14. 從政府化驗所李維傑博士在二零零二年一月七日的報告，我留意到在二零零一年十一月二十三日送抵化驗所檢驗的死者的血液中，每毫升含有 9.7 微克氯丙嗪。

15. 衞生署法醫科藍偉文醫生擬備的驗屍報告指出，氯丙嗪的致命幅度為每毫升 3 至 12 微克，由此可見，死者血液中的氯丙嗪水平已到達致命程度，初步假設他的死因是過量服用氯丙嗪是合乎邏輯的推論。

16. 不過，根據小欖精神病治療中心(治療中心)的記錄，死者在羈留期間只獲開處共五劑 50 毫克的氯丙嗪口服藥。服用時間分別為二零零一年十一月十七日下午四時和晚上七時，以及二零零一年

十一月十八日正午十二時、下午四時三十分和晚上七時。圖(2)顯示死者服藥的時間。

17. 根據治療中心的梁鑑誠先生在二零零三年三月十八日的報告，死者的體重由二零零一年十一月十四日的 84 公斤，驟降至二零零一年十一月二十二日驗屍時的 65 公斤。

18. 死者體重驟降的部分原因，可能是死者不受控制的糖尿病引致滲透性多尿，使體液大量流失。由於血液容量下降，血液中各種物質的濃度會不自然地增加。

19. 有鑑於此，我相信採用藥物代謝動力學準則進行計算，應能掌握一些有用的資料，以確定張志堅的死是否與服用過量氯丙嗪有關。

20. 在計算過程中，我曾徵詢中文大學藥劑學院左中教授，PhD 和印綺平教授，PhD 兩位同事的意見。在這類計算工作方面，她們具有豐富的經驗，可協助我撰寫本報告中涉及專門技術的部分。我的另一位同事李詠恩教授，亦曾協助我蒐集資料。她是一位十分資深的臨牀藥劑學教授。

21. 為方便計算，我們採用圖(2)和圖(3)來建立計算模式，然後把數據代入有關方程式內。雖然有跡象顯示，負責排洩氯丙嗪和美沙酮及兩者的代謝物的兩個主要器官(即腎臟和肝臟)的功能，因死者長期患有不受控制的糖尿病(藍醫生在法庭上的證供)及肝酶水平略高(伊利沙伯醫院盧文偉(譯音)醫生在二零零二年二月一日給死因裁判官的參考信)而輕微受損，但我們假定該兩個器官的功能接近正常，因為這樣輕微的受損程度應對最後的分析結果影響不大。

22. 為方便進行其後的計算工作，我們就圖(2)作出下列假設：

a. 雖然死者在二零零一年十一月十八日三次服用氯丙嗪時每次實際相隔 2.5 至 4.5 小時不等，但為方便計算，我們把相隔時間當作 4 小時。

b. 用以確定死者死後血液中氯丙嗪濃度的血液樣本是在二零零一年十一月十九日上午七時抽取的。這是一個適當時間，因為人死後，身體的新陳代謝活動會完全停止。

c. 我們假定口服及肌肉注射後的藥物代謝動力學特性相若，足以用同一藥物代謝動力學模式進行分析。

23. 死者血液在二零零一年十一月十九日的氯丙嗪濃度為 C_F，代表死者在二零零一年十一月十七日兩次服用氯丙嗪(C_1)及在二零零一年十一月十八日三次服用氯丙嗪所產生的混合效應。

24. 在計算時，我們採用了兩種方法，以便得出更全面及希望是更可靠的結論。首先，我們按時序計算結果，即是由死者五次服用 50 毫克氯丙嗪的首次服用時間開始計算的順時序方法。其次，我們根據死者死後每毫升血液含 9.7 微克氯丙嗪的水平以追溯方式計算，以便找出原來的劑量。除採用該兩種方法外，我們亦根據兩種可能出現的情況(即一次過服用相對多次服用)分析數據。

25. 有關氯丙嗪的詳細計算方法載於附件 B，計算結果撮述如下：

a. 順時序多次服用／注射：

C_F =34.56 毫微克／毫升

b. 追溯式多次服用／注射：

服用／注射次數(n) ≃ 在數學上無法計算，意即若多次服用／注射 50 毫克氯丙嗪，血液中的氯丙嗪濃度不可能達到 9.7 微克／毫升。

c. 順時序一次過服用／注射(假定死者在死前 40 小時服用／注射氯丙嗪)：

C_F =23.69 毫微克／毫升

d. 追溯式一次過服用／注射

死前 40 小時一次過服用／注射=102.4 克(102 400 毫克)，即 2 048 片 50 毫克的氯丙嗪藥片或 2 048 安瓿的氯丙嗪(每針劑量為 25 毫克／毫升 x 2 毫升)。

若假定死者在死前不久(例如 14 小時)一次過服用／注射，一次過服用／注射=56.3 克(56 300 毫克)，即 1 126 片 50 毫克的氯丙嗪藥片或 1 126 安瓿的氯丙嗪。

美沙酮

26. 美沙酮是一種合成麻醉鎮痛劑，主要療效是止痛和戒毒或作為應付毒癮的臨時代用品。

27. 服用美沙酮的主要不良影響包括壓抑呼吸、壓抑循環系統、導致神志不清、暈眩、鎮靜神經、噁心、嘔吐和出汗等。由於這種藥物對中央神經系統有潛在的壓抑作用，處方時要相當小心，對於同時服用其他可能引致中央神經系統受壓抑藥物的病人，應處以較少劑量，否則可能會導致嚴重鎮靜神經或昏迷[7]。

28. 美沙酮的藥物代謝動力學特性如下：

a. $t^1/_2$ = 48 小時[8]

b. 生物有效性=0.75[9]

c. 血漿中美沙酮致死含量=0.4 - 1.8 微克/毫升[10]

29. 根據所得資料，我知道死者曾在二零零一年十一月十七日凌晨一時至上午八時期間，於伊利沙伯醫院接受兩次美沙酮肌肉注射，每次劑量為 10 毫克。在此之前，他曾在二零零一年十一月十二日至十四日期間，多次獲處方美沙酮，每日 40 至 50 毫克不等。死者服藥的時間載於圖(3)。

30. 為方便計算，我們就圖(3)作出下列假設：

a. 假設死者是在二零零一年十一月十二日至十四日每天早上的相若時間服用三劑口服美沙酮。

b. 由於記錄並無註明，所以假設三劑藥物的平均份量均為 50 毫克。

c. 口服和肌肉注射美沙酮的藥物代謝動力學特性相若，足可採用同一模式進行分析。

d. 確定死後血含量的工作在二零零一年十一月十九日上午七時進行。

31. 有關美沙酮的詳細分析載於附件 C，結果撮述如下：

a. 順時序多次服用／注射：

C_F=118.37 毫微克/毫升(=0.118 微克/毫升)

b. 追溯式多次服用／注射：

服用／注射次數=在數學上無法計算

c. 如確定濃度的工作在二零零一年十一月十七日上午九時左右進行，則濃度=0.197 微克/毫升

對所得結果的探討

<u>氯丙嗪</u>

32. 從計算所得，在二零零一年十一月十九日上午七時左右的氯丙嗪濃度為每毫升 34.56 毫微克(每毫升 0.03456 微克)，含量大大低於可致命的每毫升 3 至 12 微克，因此，這五劑氯丙嗪應不會直接與死因有關。

33. 根據小欖精神病治療中心處方氯丙嗪的記錄，在第(25)段所載的四個分析結果中，只有結果(a)和(b)較切合實情。不過，看似最近乎真實情況的結果(a)顯然不符合化驗所的化驗結果，而結果(b)則一目了然，無需多加解釋。即使假設死者只是一次過服用了一劑氯丙嗪，結果(c)仍然不符合化驗所的化驗結果。不論從身體本身或生理角度來看，結果(d)都明顯不可能發生。即使假設肌肉注射藥物的生物有效性較口服藥物的大一倍(實際上，這亦極不可能)，死者死前 40 小時及 14 小時仍須分別接受 1 024 安瓿及 563 安瓿氯丙嗪；這從身體本身或生理角度來看，亦同樣不可能發生。

34. 基於上述理由，引致血漿的氯丙嗪濃度達到每毫升 9.7 微克的可能性如下：

a. 正如小欖精神病治療中心梁鑑誠先生推測，原因可能是不受控制的糖尿病導致脂肪組織細胞破裂(脂肪分解)，因而釋放出大量原來儲存於該處的氯丙嗪。雖然這種情況有可能發生，而且梁先生亦提供了相關和足夠的醫學文獻，但必須指出的是，這純粹是理論上的解釋，最好還是通過實驗求證，證明不受控制的糖尿病引致的脂肪分解，確實會造成這樣的死後血漿濃度。

b. 不受控制的糖尿病導致體液流失，產生血濃縮效應，從而減低血容量，令物質的血濃度提高。

c. 死後藥物濃度重新分布，從濃度較高的儲存組織流向濃度較低的地方，例如血液。

d. 上述某些項目或全部項目的混合效應。

美沙酮

35. 在二零零一年十一月十九日上午七時和二零零一年十一月十七日約上午九時計算所得的美沙酮濃度，分別是每毫升 0.118 微克和每毫升 0.197 微克，均較每毫升 0.4 至 1.8 微克的致死劑量為低，因此該五劑美沙酮應不會直接與死因有關。

36. 根據二零零二年一月七日政府化驗所的化驗結果，死者血液的毒理分析顯示血液中的美沙酮水平為每毫升 0.88 微克，含量達致死劑量範圍。不過，屍體血漿有這樣高的美沙酮水平是不合常理的，因為死者並無進一步服用美沙酮的記錄。

37. 基於缺乏實質的證據，最合理的解釋是屍體血液樣本(即使從外圍抽取)的藥物濃度，通常會遠高於死的時候血漿中的藥物濃度，死亡和驗屍時間如已相距數日，更會出現這種情況，因為屍體會出現第 34(c)段所述的藥物濃度重新分布的現象。此外，就氯丙嗪而言，其他可能性亦必定存在。因此，我們難以把屍體血液中報稱的藥物濃度和文獻數值所載的濃度作一比較。[11]

整體結果

38. 從計算所得，似乎氯丙嗪和美沙酮的個別效應對死者致死的原因，影響極為輕微，因為死者服用兩種藥物的劑量，尚未達到足以致命的程度。不過，同時服用兩種藥物很可能導致副作用加劇，令中樞神經系統的抑制作用增強，以致極度昏睡和思想混亂。在藥物效應增強下，受害人遇到危難時，精神和肉體都不能迅速作出反應。

39. 此外，我擬就二零零三年六月十一日信件內提出的其他事宜作出回應：

a. (1)和(2)已在上述討論中加以闡述。

b. 氯丙嗪能產生很強的抗膽碱能效力和腎上腺素受體阻斷效力。[3] 前者通常會造成瞳孔擴大，後者則會造成瞳孔縮小。不過，在極度過量服用氯丙嗪後，最顯著的反應是瞳孔縮小。[12, 13]

c. 服用／注射乙醇後，在尿液中出現乙醇一般所需的時間差別很大，主要視乎實際服用／注射的化學物分量而定。一般而言，乙醇約需一小時經腸臟吸收，然後進入血液。其後血液濃度會隨時間下降。經吸收後，身體約需兩小時才能把一杯 12 安士的啤酒排掉。[13]

摘要和結論

40. 我們已通過建立藥物代謝動力學模式，模擬真實的情況，從而計算氯丙嗪和美沙酮的服用劑量。

41. 我們的分析結果並未顯示死者所服用藥物的劑量和其死亡有直接關係。

42. 雖然屍體血液中藥物的水平達到報稱的致死劑量範圍，死者不受控制的糖尿病引發脂肪分解作用的可能性仍然存在，但這一點須從實驗研究取得輔助證據才能證實。其他可能性包括血濃縮效應和藥物濃度在屍體內重新分布。

43. 同時服用兩種藥物產生的混合效應，令死者不受控制的糖尿病所潛伏的性命危機，加添危險因素。

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(從略)

(簽署)　　二零零三年六月二十三日

李炯前　　(日期)

[本文以英文版為準]

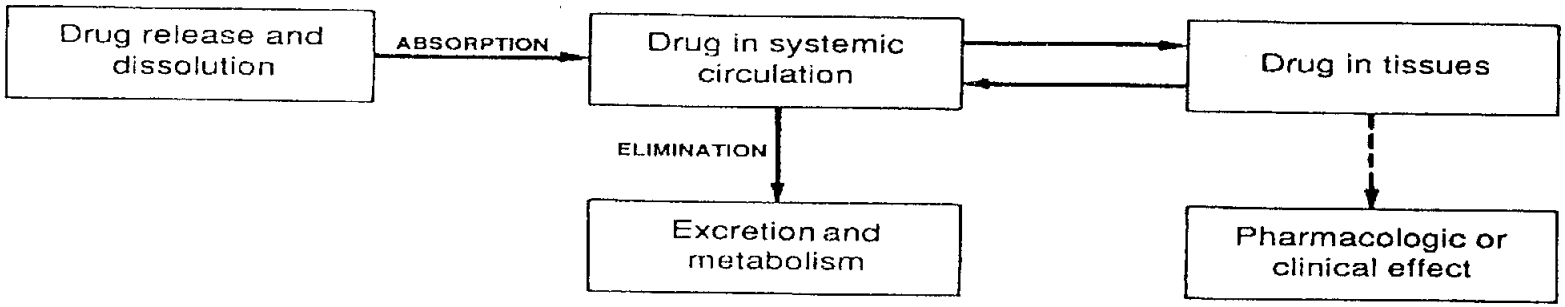

Figure 1. Relationship between the drug, its original product and the pharmacologic effect[1]

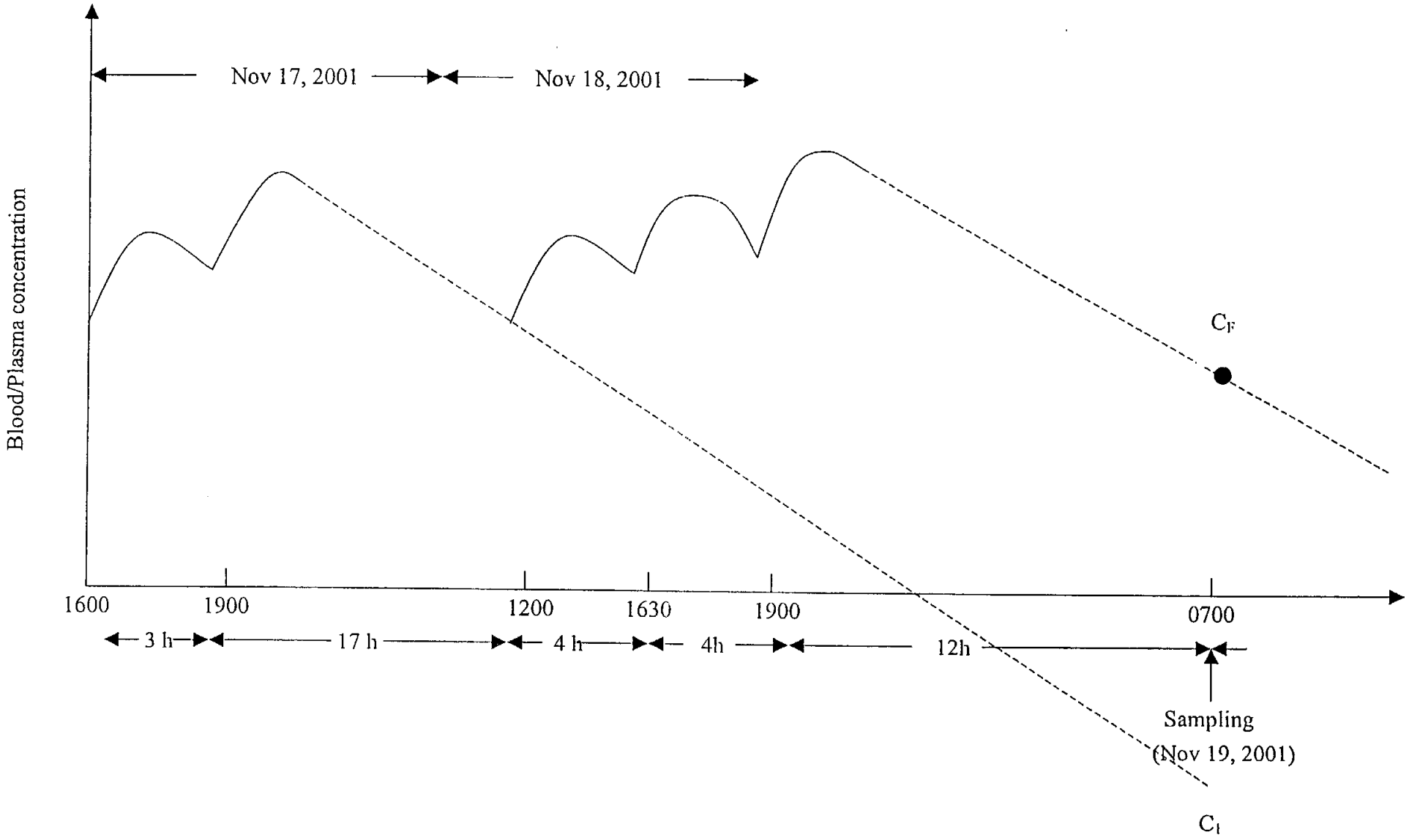

Figure 2 : Administration of Chlorpromazine

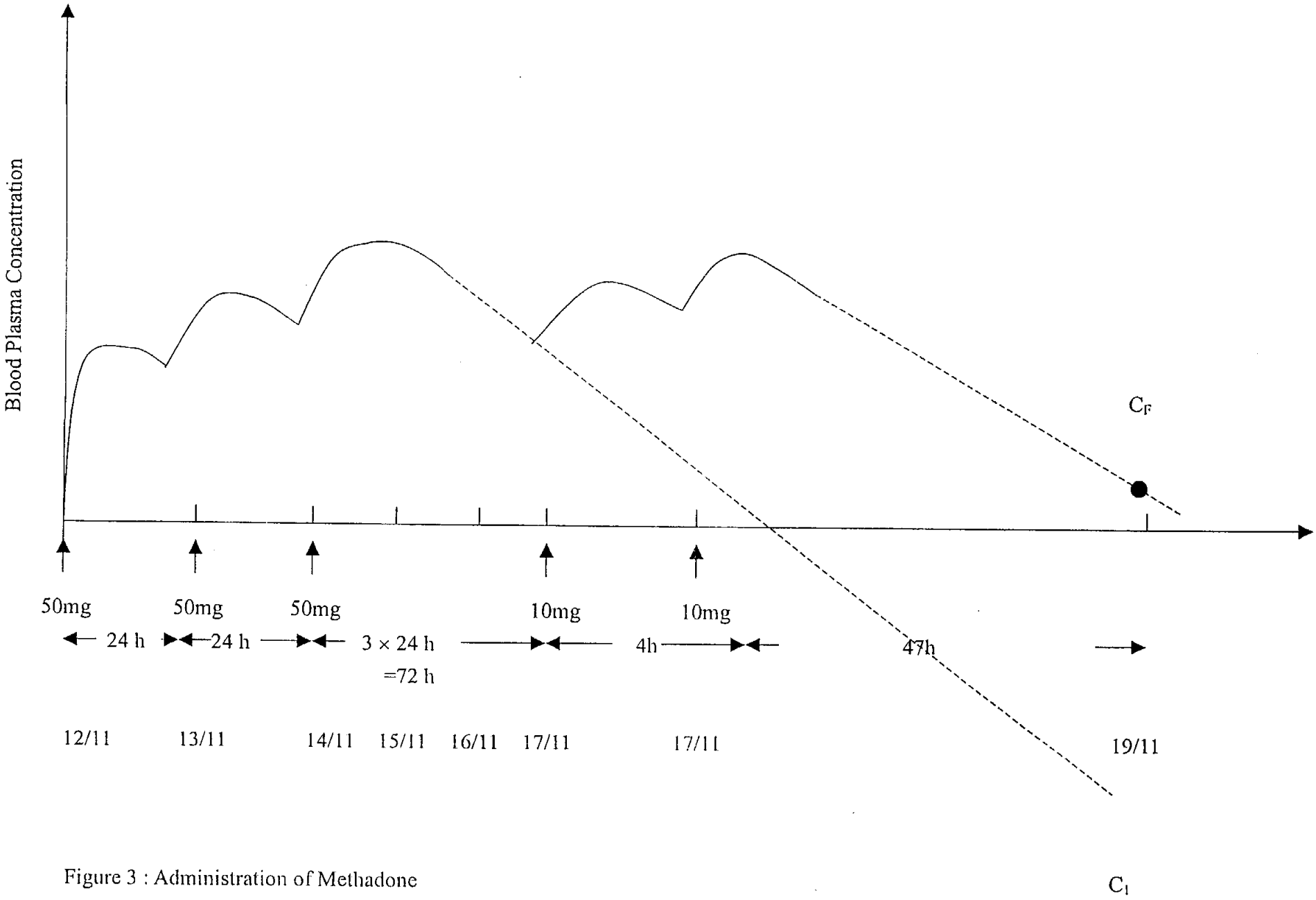

Figure 3 : Administration of Methadone

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

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1. Lee KKC, Pharmaceutical Studies of Epirubicin Emulsion, MPhil thesis, May 91
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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
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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
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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.
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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

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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

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

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

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

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

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

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

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

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