DIRECT MEASUREMENT OF CHLORMETHIAZOLE EXTRACTION BY LIVER, LUNG AND KIDNEY IN MAN

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- 1 Chlormethiazole was used as a basal sedative for patients undergoing angiographic procedures.
- 2 Blood samples were drawn opportunistically to examine chlormethiazole extraction across liver, lungs and kidney.
- 3 Extraction across liver was typically 70–80% and apparently unrelated to input concentrations. Evidence for extraction across lung and kidney was inconclusive but these could each be approximately 20%.
- 4 Pharmacokinetics of chlormethiazole derived from compartment models were in accord with previous reports and were characterised by a high total body clearance (1–1.5 l/min).
- 5 Postural changes associated with the radiological procedures caused fluctuating blood concentrations which appear as noise in curve fitting procedures.
- 6 Pharmacokinetic properties derived from compartment theory cannot cope with these perturbations because of the restriction imposed by time averaging (i.e. mean clearances, half-lives and volumes are produced). Systematic studies of pharmacokinetic properties of perfusion-limited drugs such as chlormethiazole must be developed in such a way as to allow for independent variation of flow and extraction.

Introduction

Chlormethiazole ethanedisulphonate (CTZ) (Hemineurin or Heminevrin, Astra Pharmaceuticals Pty. Ltd) is a central depressant and anticonvulsant agent which has been used in the treatment of alcoholic delirium tremens (Glatt, George & Frisch, 1965), pre-eclampsia (Duffus *et al.*, 1969) and as a sedative hypnotic in the elderly (Magnus, 1978). Recently, its use has been advocated as a basal sedative to accompany regional or neural blockade in the provision of balanced anaesthesia for minor surgery (Schweitzer, 1978; Mather & Cousins, 1980).

As a result of new techniques and technological developments over the past decade, there has been a rapid increase in the number of angiographic and endoscopic procedures. These procedures do not require traditional general anaesthesia but it is desirable that the patient be rendered sedated and amnesic whilst remaining rousable and co-operative. These are similar requirements to those for supplementation of neural blockade procedures. At present drugs such as diazepam are widely used for this purpose (Gjessing & Tomlin, 1977). However, recovery from diazepam is typically slow due to its pharmacokinetic

properties of long half life and low clearance (Klotz *et al.*, 1975).

The pharmacokinetics of CTZ have been described in healthy volunteers and in patients (Jostell, Agurell, Allgen *et al.*, 1978, Jostell; Agurell, Hollister *et al.*, 1978; Moore *et al.*, 1975; Nation *et al.*, 1976; Pentikainen, Neuvonen & Jostell, 1980; Seow, Mather & Roberts, 1981). The two important points consistently observed throughout all of these studies are that the total body clearance of CTZ is high (approximately equal to total liver blood flow in normal man) and that negligible amounts of unmetabolised CTZ are excreted in urine. From this information it has been deduced that the primary site of CTZ clearance is the liver, and that the hepatic extraction ratio must be high to account for the magnitude of the clearance.

To examine this deduction critically we have made a number of opportunistic measurements of CTZ extraction across the liver and other organs in patients in whom CTZ was used as the basal sedative for their angiographic procedures; in addition, pharmacokinetic constants were determined in each patient

by traditional methods. To our knowledge these observations represent the first attempt to measure organ extraction for an intravenous sedative agent in man.

Methods

Patient selection and preparation

The subjects of this study were six patients undergoing diagnostic and therapeutic angiographic procedures. One patient (number 6) was studied twice, 2 weeks apart. A synopsis of their relevant features is given in Table 1. Catheters were placed in accordance with normal clinical practice. Opportunistic use was made of these to sample blood for CTZ analyses. A number 5 French double lumen catheter was placed in each patient via the antecubital fossa and advanced into the superior vena cava. The proximal tip resided adjacent to the right atrium and was used for obtaining blood samples. The distal tip (14 cm away) was used for CTZ infusion.

Chlormethiazole infusion

Chlormethiazole ethanedisulphonate was infused as a 0.8% solution using a two stage loading and maintenance regimen designed to produce a blood concentration (CTZ base) of 4–6 mg/l in the maintenance phase (Mather & Cousins, 1980). A loading infusion of approximately 300 ml/h generally for 30–40 min was followed by a maintenance infusion, typically 80 ml/h, for the desired duration of the procedure. However these rates were modified according to the patient response (Table 1) and were not influenced in any way by the study.

Chlormethiazole determinations and calculations of organ extraction

Whole blood concentrations of CTZ (base) were determined by gas chromatography with nitrogen selective detectors, bromethizole internal standard and the generalised basic drug extraction procedure of Mather & Tucker (1974). The analytical method was sensitive to 0.01 mg/l and gave coefficients of

Table 1 Characteristics of patients studied and details of their infusion regimens

Study	Age (years)	Sex	Weight (kg)	Height (cm)	Procedure/treatment	CTZ infusion*
1	58	F	63	158	Renal, hepatic and IVC angiography. Grawitz tumour left kidney, no hepatic pathology.	(a) 380(31) (b) ~0†
2	46	F	65	173	Renal angiography. Benign angiomyolipoma of right kidney.	(a) 380(30)† (b) 75(64)†
3	59	M	65	173	Hepatic arteriography for disseminated hepatic metastases from colonic carcinoma.	(a) 299(40) (b) 80(96)
4	71	M	66	173	Hepatic arteriogram and cyanoacrylate embolisation of benign hepatic artery tumour.	(a) 299(40) (b) 80(8) (c) 299(12) (d) 80(41) (e) 299(10) (f) 80(66)
5	70	F	69	?	Transhepatic portography for embolisation of oesophageal varices in left gastric and short gastric veins.	(a) 299(30) (b) 80(80) (c) 299(15) (d) 80(69)
6	52	F	68	170	Main stream aortography and left renal arteriography. Left suprarenal tumour.	(a) 299(60) (b) 80(64)
6a		As 6, 2 weeks later			Adrenal arteriography. Gelfoam embolisation of left suprarenal tumour.	(a) 299(60) (b) 80(130)

* ml/h infusion rate (min infused at that rate); read in conjunction with Figure 1.

† pump failure occurred. Exact dose uncertain during this period.

Figure 1 Blood concentrations of chlormethiazole in patients undergoing angiographic procedures. Read in conjunction with Table 1. ● SVC, □ arterial renal, ■ venous renal, ○ arterial hepatic, ▲ venous hepatic. ↑ start of infusion, ↑* end of infusion.

Table 2 Extraction of chlormethiazole by liver, kidney and lung

Study	Input concentration ¹ range (base mg/l)	Liver ²	Kidney ³	Lung ⁴	Comments
1	2-3	30-70% (<i>n</i> = 2)	Right 20% (<i>n</i> = 1) Left 10% (<i>n</i> = 1)	~30% (<i>n</i> = 2)	Left kidney tumour
2	1-2	70-90% (<i>n</i> = 4)	~20% (<i>n</i> = 3)	~0 (<i>n</i> = 5)	Major postural changes ~75 min
3	3-5	10-50% (<i>n</i> = 6)	N.D.	10-20% (<i>n</i> = 6)	Major postural changes ~130 min
4	2-5	70-80% (<i>n</i> = 4)	N.D.	~0 (<i>n</i> = 4)	Major postural changes 70 and 120 min
5	3-8	60-70% (<i>n</i> = 11) ⁵	N.D.	N.D.	Patient restless and moving at ~90 to 180 min CTZ conc. in portal vein ~SVC
6	9-15	70-80% (<i>n</i> = 11)	N.D.	~0 (<i>n</i> = 8)	Major postural changes ~90-100 min
6a	4-6	10-30% (<i>n</i> = 6)	N.D.	~0 (<i>n</i> = 8)	Jaundiced

N.D. = Not determined

1 = Concentration range (base, mg/l)

3 = Arterial → renal vein

5 = SVC → hepatic vein

n = number of observations

2 = Arterial → hepatic vein

4 = SVC → arterial

variation of 3-5% over the concentration range encountered. Standard curves were linear and passed through the origin. Extraction ratio (ER) was determined for each organ (where appropriate) by Equation (1) where C_{in} and C_{out} are input and output concentrations respectively.

$$ER = \frac{C_{in} - C_{out}}{C_{in}} \times 100\% \quad \text{Equation 1}$$

In all seven studies, ER across the liver was determined directly (artery or superior vena cava (SVC) to hepatic vein); in two studies ER across the kidney (artery to renal vein) was determined directly, and in one study ER across the gut (artery to portal vein) was determined directly. In six studies, extraction across lung was assessed indirectly (SVC to artery). The results obtained must be viewed in the light of the fact that many of the measurements of ER were not made at steady-state due to the demands of the procedures performed.

Calculation of pharmacokinetic constants

Equally weighted serial SVC blood concentration-time data were fitted to empirical biexponential equations as described by Mather, Ringrose & Austin (1979). A biexponential expression was used since previous pharmacokinetic studies indicated that this was generally adequate to characterise CTZ blood concentration-time data. In several instances the biexponential equation collapsed to a mono-

exponential. Pharmacokinetic constants were derived from the coefficients and exponents of the exponential equations as described by Wagner (1976). It should be noted that CTZ loss into the plastic tubing of administration sets occurs to the extent of up to 30% (Pentikainen *et al.*, 1980; Runciman *et al.*, 1981; Tsuei, Nation & Thomas, 1980). This produces an uncertain effect on dose which can lead to total body clearance and volumes of distribution of CTZ being overestimated by a similar factor.

Results

Clinical management of patients

From a clinical viewpoint the chlormethiazole infusions were satisfactory in that they generally produced a state in which patients were calm, drowsy yet rousable with little recollection of the procedure. However, to achieve these conditions, infusion rates needed several adjustments in some patients (Table 1).

Organ extraction of chlormethiazole

Individual blood concentration-time curves (Figure 1) and data in Table 2 indicate that CTZ was always extracted across the liver. Bearing in mind that these measurements were not always made with steady

Table 3 Derived pharmacokinetics for chlormethiazole given by intravenous infusion

Study	CL ¹ (l/min)	V ² (l)	V _{SS} ³ (l)	T _{1/2} α ⁴ (min)	T _{1/2} β ⁵ (min)	Comments
1	2.0	48	48	0	163	1 compartment model. Uncertain dose during maintenance infusion. Underestimate of T _{1/2} β
2	6.4	266	266	0	287	1 compartment model. Uncertain dose during both periods.
3	1.1	41	233	12	254	2 compartment model.
4	1.4	326	326	0	163	1 compartment model.
5	1.0	152	186	55	153	2 compartment model. Marked blood concentration fluctuations. Poor estimate of T _{1/2} α.
6	0.5	32	151	11	260	2 compartment model.
6a	0.1	41	642	8	~5000	2 compartment model with deficient elimination. Greatly diminished hepatic function probably due to concurrent chemotherapy. Severely jaundiced at time of study.

¹Total body clearance (blood).²Initial dilution volume.³Steady-state volume of distribution.⁴Fast half-life.⁵Slow half-life.

state conditions, an average of 70–80% extraction was observed. This was apparently independent of the input concentration, even in patients with hepatic lesions (e.g. numbers 3 and 4). In the case in which the values were significantly lower (10–15%) (6a) the patient was jaundiced and liver function tests confirmed severe hepatocellular dysfunction. In other cases, individual observations of extraction were high and even exceeded 90%. Renal extraction was assessed in two subjects with unilateral kidney lesions, and although only five observations were made, these suggest that the kidney can remove CTZ. Unfortunately urinary excretion of CTZ was not measured in these patients so that it cannot be assessed whether there was excretion into urine or biotransformation in kidney. Extraction by lung to the extent of 10–20% possibly occurred in studies 1 and 3. However these observations require confirmation by direct measurement of pulmonary artery to systemic artery gradients at steady-state. In the one case measured, arterial to portal vein gradients were zero, indicating no net extraction across the gut.

Systemic pharmacokinetics of chlormethiazole

Derived pharmacokinetic constants (Table 3) indicate high total body clearance and extensive extra-

vascular distribution of chlormethiazole. Blood concentration-time data for Patients 1, 2 and 4 were adequately described by a monoexponential equation while those for the remaining patients required a biexponential equation. Unfortunately, pump malfunction during studies 1 and 2 caused uncertainty in the total dose given and resultant uncertainty in total body clearances and volumes of distribution for these studies (apart from any systematic overestimates of these variables due to CTZ loss into the plastic tubing of the administration sets). Study 6a indicated extremely low clearance. As noted previously this case of defective elimination was the probable consequence of concurrent chemotherapy for an inoperable suprarenal tumour.

Discussion

In keeping with previous observations (Schweitzer, 1978; Mather & Cousins, 1980) chlormethiazole provided generally satisfactory basal sedation and amnesia for these procedures. However, it is our feeling that several patients may have been more comfortable had slightly deeper levels of sedation been achieved.

The results of this study confirm the deductions

made on the basis of high total body clearance and low urinary excretion of CTZ, i.e. that hepatic extraction must be high to account for the magnitude of the total body clearance. Because total body clearance is given by the summed products of extraction ratio and blood flow for each organ, even a small pulmonary extraction can have a marked effect on total clearance because of the high pulmonary blood flow. Renal clearance would have a smaller effect because kidney blood flow is only ~20% of cardiac output. Since urinary excretion of CTZ is negligible, renal clearance has to be interpreted as renal metabolism. However, these suggestions of extraction by lung and kidney await confirmation in systematic studies and should only be regarded as preliminary observations at this stage.

With the exception of the two studies where pump malfunction occurred, the derived systemic pharmacokinetic constants for chlormethiazole are consistent with previous reported data (e.g. Nation *et al.*, 1976; Pentikainen *et al.*, 1980). In particular, total body clearance related well to the extent of extraction by liver and the other organs.

However, it is obvious that there are limitations to the confidence with which the data may be interpreted in an opportunistic study such as this. As the contribution of any organ to drug elimination is dependent

on both extraction ratio and blood flow, and as drug distribution is also dependent on blood flow, it would be desirable for regional blood flow to remain fairly constant for the period of the study. In fact, in this study, there were marked changes in blood concentration of chlormethiazole in association with changes in posture necessitated by the procedure, and although all data were assumed to be equally valid for the purposes of curved fitting, this assumption would obviously give rise to inaccuracies.

In order that opportunistic studies such as this may be interpreted with a greater degree of confidence, we have developed an animal model in which blood flow through, and drug extraction across, heart, lungs, liver, kidney and gastrointestinal tract may be measured directly at frequent intervals (Runciman, Ilesley & Mather, 1979). Direct measurements of rates of drug elimination may then be compared with those derived from a classical compartmental method, and the effects of haemodynamic disturbances such as anaesthesia or haemorrhage on drug disposition may be examined in detail. Limitations on the accuracy of the compartmental method under different circumstances may then be evaluated critically.

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