Relationship between plasma concentrations of clonidine and mean arterial pressure during an accidental clonidine overdose

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The time course of toxicity in a 28 year old man following a 100 mg accidental overdose of clonidine hydrochloride is compared with the decline of plasma clonidine over 5 days. The concentration data were analyzed by nonlinear least squares regression, and fitted to a model which dissociated the blood pressure effects into pressor and depressor components. According to this analysis, there appeared to be two phases of toxicity over time—a hypertensive, and a hypotensive phase. The hypotensive and the hypertensive phases may result primarily through differential stimulation of central α_2 -, α_1 -, and vascular post-synaptic α_2 -adrenoceptors as plasma concentrations fall.

Keywords clonidine overdose plasma concentrations pharmacokinetics

Introduction

The hypotensive response of clonidine is thought to arise predominantly from stimulation of central α_2 -adrenoceptors (Kobinger, 1978), but clonidine also stimulates vascular postsynaptic α_2 -adrenoceptors (Baum, 1984) and in higher concentrations, α_1 -adrenoceptors which oppose the hypotensive action. Differential stimulation of these receptors may result in the presence of a therapeutic window which may be seen both upon single dose and chronic administration (Frisk-Holmberg *et al.*, 1984; Wing *et al.*, 1977b).

Clonidine overdose may be associated with a variety of symptoms and by the occurrence of both hypotension and hypertension. However, no clearly discernible relationship has been demonstrated between ingested dose and the presence or absence of clinical signs (Conner & Watanabe, 1979). In this case study, we report

on the relationship between plasma concentrations of clonidine and blood pressure in a 28 year old male who took 100 mg clonidine, utilizing a pharmacokinetic model which dissociates these two opposing effects (Paalzow & Edlund, 1979; Frisk-Holmberg *et al.*, 1984).

Case report

The patient was a previously healthy 28 year old male who accidentally ingested 100 mg of clonidine in powdered form. He had intended to take a dose of 0.1 mg from a laboratory source which was not approved for human use, but due to a weighing error he took 1000 times the intended dose. His past medical history was significant only for borderline hypertension; 1 week previously he was noted to have a blood pressure

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of 140/90 mm Hg by sphygmomanometry during routine medical examination. Thirty minutes following ingestion, the patient presented to the Emergency Service where he was found to have a blood pressure of 200/140 mm Hg, a respiratory rate which fell rapidly to 4–6 min⁻¹, a pulse rate of 30 beats min⁻¹, and a rectal temperature of 96.9° F. He was disoriented to place and time.

Gastric lavage was instituted, he was intubated and placed on a ventilator. Gastric contents were subsequently analyzed. Following 1 mg atropine i.v. the pulse rose to about 70 beats min⁻¹. A subclavian CVP and an antecubital intravenous line were placed, and normal saline was infused. He was transferred to the intensive care unit where he was treated for the next 72 h. About 12 h after ingestion, when the blood pressure was 170/120 mm Hg, tolazoline was administered i.v. When approximately 10 mg had been infused, the blood pressure fell to about 70/20 mm Hg with the pulse increasing from 63 to 75 beats min⁻¹. Tolazoline was discontinued, and dopamine was infused at a rate of 5 µg kg⁻¹ min⁻¹ initially. This resulted in a blood pressure of 140/100 mm Hg and it was tapered over 15 min. No additional tolazoline was given. Other medications administered included atropine sulphate 0.5 mg i.v. at 8 h, frusemide 10 mg i.v. 8 times between 1.5 and 28 h, aminophylline 300 i.v. every 6 h until 62 h, and ammonium chloride.

There appeared to be a biphasic course of toxicity. A hypertensive phase lasting 24 h was followed by a hypotensive phase as plasma concentrations of clonidine fell. Associated with hypertension were respiratory depression, bradycardia, ileus, mydriasis, and a mental status which ranged from coma to delirium characterized by agitation, disorientation to time and place, visual hallucinations and paranoid ideas. Amnesia for events during this time was later evident.

A hypotensive phase lasted from approximately the end of day 1 until midway through day 3 and was associated with a heart rate of 60–70 beats min⁻¹, sedation, and the onset of miosis. The paralytic ileus and respiratory depression continued but resolved during this time, allowing extubation at the end of day 3. Midway through day 4 when symptoms had appeared to clear, the patient suddenly exhibited tachycardia, hyperventilation, diaphoresis, anxiety and abdominal cramps. Although abdominal findings were unremarkable, a fine bilateral tremor of the hands was noted. These symptoms which lasted approximately 12 h were similar to those described as occurring during clonidine withdrawal (Reid *et al.*, 1977).

Methods

Clonidine measurements were made on small aliquots of plasma which had been drawn for clinical reasons. Seventeen samples were subsequently analyzed, giving rise to plasma concentrations of clonidine between 50 min and 127 h following ingestion. Clonidine was assayed by radioimmunoassay (RIA) as described by Arendts *et al.* (1979) using a ¹²⁵I tracer. Pharmacokinetic analysis was performed by nonlinear least squares regression to polyexponential equations and optimal exponentials were determined according to the method of Boxenbaum *et al.* (1974). The plasma data were used in conjunction with the blood pressure measurements obtained clinically during the course of care to provide a model for the relationship between plasma clonidine and mean arterial pressure as described by Paalzow & Edlund (1979). The times during which tolazoline and dopamine were given were deleted from the analysis. All blood pressure measurements which are used in this study were obtained by sphygmomanometry with the patient in the supine position.

Results

Of 100 mg clonidine ingested, gastric lavage removed 57 mg. Plasma concentrations rose rapidly, achieving 230 ng ml⁻¹ within the first hour. Subsequently, plasma concentrations fell in a biphasic manner. The first phase was complete within the first day; thereafter, plasma concentrations fell exponentially with a half-life of 12.2 h, as shown in the top inset of Figure 1.

There was a complex relationship between plasma clonidine concentrations and mean arterial pressure. The upper panel of Figure 1 shows the time course of mean arterial pressure; a predominantly hypertensive phase in the first 24 h was followed by a more prolonged phase characterized by mild hypotension. The bottom panel shows the relationship between plasma clonidine concentration and mean arterial pressure. Above approximately 50 ng ml⁻¹, there was a hypertensive response; below 50 ng ml⁻¹ a mild hypotensive reaction was seen. This relationship may be made explicit through a model which involves a concentration-response of both a pressor and depressor effect:

$$\text{MAP} = \frac{90 \times C^{S_1}}{C^{S_1} + \frac{1}{Q_1}} - \frac{40 \times C^{S_2}}{C^{S_2} + \frac{1}{Q_2}}$$

MAP is the mean arterial pressure. C is the plasma concentration of clonidine, S₁ and Q₁,

Figure 1 Time course and concentration-response curve of plasma clonidine on mean arterial blood pressure

Inset a) Plasma clonidine concentrations fell biphasically with an initial 'half-life' of 2.18 h, followed by an elimination phase half-life of 12.2 h.

Insets b) and c) Parameters for the model described by equation (1) (with associated nonlinear least squares standard deviation in parentheses) are $S_1 = 2.14$ (0.37), $Q_1 = 0.000122$ (0.000212), $S_2 = 1.01$ (0.600), $Q_2 = 0.0667$ (0.113). r^2 of the model is 0.616.

S_2 and Q_2 are parameter constants fit to pressor and depressor components of clonidine (see accompanying figure). Although a brief hypotensive phase is predicted to occur as plasma concentrations rise to hypertensive levels, no such phase was seen in this patient, who arrived at the emergency room beyond the predicted time for initial hypotension.

Discussion

In this case of a 28 year old man with a 100 mg clonidine overdose, there was a biphasic blood pressure response over time. This response was modelled by dissociating the pressor and depressor components of clonidine, and fitting the concentration time course of clonidine in plasma to the measured blood pressure seen during the course of toxicity. According to this analysis, the highest plasma concentrations of clonidine maximally stimulated both pressor and depressor components, and a balance between these two actions resulted in hypertension. As plasma concentrations of clonidine fell, the pressor component was reduced, leaving the depressor component relatively unopposed, and hypotension resulted.

There appeared, however, to be a relative shift of each phase to higher clonidine blood concentrations than would be expected on the basis of previous results using therapeutic doses. This shift may be a result of multiple factors, including differences in analytical technique in measuring the drug, chronic versus acute administration, the presence of other medications, or underlying hypertension (Wing *et al.*, 1977a, b; Frisk-Holmberg *et al.*, 1984). The possibility of acute tolerance and withdrawal following an overdose has been predicted, but has not been substantiated to date (Connor & Watanabe, 1979). The relative rightward shift of the concentration-effect curve and the presence of withdrawal-like symptoms suggest this possibility, but contrary to expectation, rebound hypertension was not observed. Additional observations are required to determine whether these factors have contributed to the present findings.

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