to low cranial concentrations. However, any agitation of the CSF, as for example during coughing, could result in very high concentrations reaching the brain earlier, with consequent severe respiratory depression (Kafer et al., 1983).

Little work has been directed at intrathecal morphine, possibly because the extradural route seems to be a safer alternative. However, it would seem logical to inject very small doses of opiates directly to the active compartment, namely the subarachnoid space. King, Mok and Steen (1981) found no respiratory depression in 440 patients after 400 µg of intrathecal morphine, but even this dose could theoretically produce CSF concentrations in the order of 300 ng ml⁻¹. If the average volume of human CSF is approximately 175 ml and the desired lumbar CSF morphine concentration not more than 40 ng ml⁻¹, then an appropriate intrathecal dose would be just 5 µg of morphine!

Finally, we must state that our technique of assaying morphine in this study proved both costly and time-consuming. A more practical method of studying the problem would be the use of unlabelled morphine and high pressure liquid chromatography for drug concentration measurement. Further studies along these lines are in progress.

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REFERENCES


HISTORIC FIRST: ACUTE TOLERANCE TO THIOPENTONE IN MAN

Sir,—Toner and colleagues (1980) state that "Dundee, Price and Dripps (1956) described a phenomenon which they called 'acute tolerance to thiopentone.'" The tacit inference of discovery is wide of the mark: priority lies elsewhere.

Some seven years earlier, Mark, Papper, Brodie and Rovenshtein (1949) reported that "... evidence of an acute tolerance to pentothal (sc) was found in man. When a subject was maintained at high plasma concentrations of the drug, the signs of anesthesia reappeared at higher plasma levels than when he was maintained at low plasma concentrations." Indeed, figure 1 shows that, by extrapolation from curve BB, "3.25 g in 52 min" to curve AA, "2.0 g in 5 min", awakening after the larger dose occurred at plasma drug concentrations corresponding to deep anesthesia in the same subject after the smaller dose. This preliminary account was subsequently recorded in extenso (Brodie et al., 1951). Dundee, Price and Dripps (1956) later verified the occurrence of acute tolerance to thiopentone in patients receiving smaller doses (2–15 mg kg⁻¹).

All of these studies in man were antedated in the dog by Shideman, Kelly and Adams (1948), who noted a form of acute tolerance to thiopentone under somewhat altered conditions: when doses of 10 mg kg⁻¹ were repeated at short intervals after apparently complete recovery from the depressant effects of the previous dose, the plasma concentrations at which the righting reflex returned were successively higher with each additional dose.

In point of fact, the finding of acute tolerance to thiopentone in man resulted serendipitously from investigations (Mark et al., 1949; Brodie et al., 1951) originally designed to correlate clinical signs of anesthesia with plasma concentrations of thiopentone.

![Fig. 1. Plasma concentrations and the signs of anaesthesia after two different doses of thiopentone in the same subject. (From Mark et al., 1949.) AA = 2 g in 5 min; BB = 3.25 g in 52 min. 1 = Corneal reflex; 2 = conjunctival reflex; 3 = eyeball motion; 4 = orientation.](https://academic.oup.com/bja/article-abstract/56/8/922/241390/0)
Acute tolerance rendered the effort futile: except for very low or very high concentrations, a single plasma concentration conveys little or no information about depth of anaesthesia with thiopentone. Nevertheless, this was the first demonstration of acute tolerance to thiopentone in man.

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REFERENCES

Sir,—It is not the intention of my colleagues or me to deny any priority to the team of workers from New York University, New York, which included both Dr Lester Mark and Dr B. B. Brodie, to whom credit must go for the first demonstration of acute tolerance to thiopentone in man.

The paper by Toner and colleagues (1980) was simply a report, using modern methods of drug analysis and a larger number of patients, to confirm the findings in our earlier study (Dundee, Price and Dripps, 1956) which was carried out on only 16 patients. We did refer to two of the New York papers in our 1956 publication—Brodie (1952) and Brodie, Mark, Papper, Lief, Bernstein and Rosenstine (1950)—but missed the previous paper by Mark, Papper, Brodie and Rosenstine (1949). I can only assume that this omission can be attributed to the fact that the title of the paper was “Quantitative Pharmacological Studies with Pentothal” and that it was published in the N. Y. State Journal of Medicine rather than in a more widely read anaesthetic or pharmacological journal.

Dr Mark points out that the finding of acute tolerance to thiopentone in man resulted from investigations designed to correlate clinical signs of anaesthesia with plasma concentrations of the drug. Our initial study was an attempt to explain why patients could be anaesthetized in North America with doses which at that time (1955-56) were half of those in current use in Great Britain. It was almost uncanny to find that two groups of workers, quite independently, came to the same conclusions and that both reached these when trying to correlate a clinical experience with the drug with plasma concentrations.

It is over a quarter of a century since the early papers on acute tolerance to thiopentone appeared in the anaesthetic literature and it is only recently that any doubt has been cast on the existence of this phenomenon (Stanski et al., 1980). There is no doubt that the phenomenon, as demonstrated by plasma concentrations, does exist and one would welcome a satisfactory explanation as to the underlying mechanisms.

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REFERENCES

ACCIDENTAL ADMINISTRATION OF ADRENALINE DURING I.V. REGIONAL ANAESTHESIA

Sir,—A 50-year-old lady (65 kg) underwent surgery for carpal tunnel syndrome of her right hand under i.v. regional anaesthesia. Her heart rate and arterial pressure were monitored conventionally, and were virtually unchanged throughout the operation, ranging between 80 and 85 beat min⁻¹ and 140/85 to 150/85 mm Hg.

A standard technique was used for the i.v. regional anaesthesia (Bier, 1908; Holmes, 1963, 1980; Eriksson, 1969), the tourniquet being inflated to 300 mm Hg. Lignocaine 0.5% 30 ml was injected to the venous system, through a peripheral venous cannula. Complete anaesthesia was established in 20 min. The operation lasted for 15 min. After that the cuff was deflated slowly to avoid any reaction following the release of lignocaine into the general circulation.

As the circulation re-established, the forearm became covered with a deep red rash, while the fingers became swollen, cyanosed and very cold.

Realizing that the angiospasm was caused by the accidental administration of adrenaline (the injected solution was made up of 0.5% lignocaine with adrenaline 1:80000), we immediately administered the α-adrenergic blocker phenotolamine in a dose of 10 mg i.v.

In 30 min the circulation to the arm was restored, as was apparent by the subsequent regression of the symptoms. Meanwhile, arterial pressure was slightly decreased to 120/80 mm Hg.

It is well known that the solution used for i.v. regional anaesthesia must not contain adrenaline or any other vasoconstrictor, because of the necrosis of the extremity which may follow intense angiospasm. However, if accidental administration of an α-adrenergic stimulant does occur, its reversal with an α-blocking drug may be of use.

We are concerned as to the most appropriate route by which the α-adrenoceptor antagonist should be administered under such circumstances, and would value the advice of your readers.

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