ACCIDENTAL SUBARACHNOID INJECTION OF GALLAMINE

A Case Report

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SUMMARY

Accidental subarachnoid injection of gallamine and its management is reported. Methods of identification of the drug in the c.s.f. are described. Early treatment should be initiated, since the drug was still identifiable in the c.s.f. after 90 min. Removal of the c.s.f. and sedation may have prevented a fatal outcome in our patient.

We report the management of a patient who received an accidental injection of gallamine triethiodide into the subarachnoid space. The earliest reference to the central effects of gallamine in man is contained in a single sentence: “There is also some clinical evidence that, when injected intrathecally in human subjects gallamine triethiodide produces convulsions” (Dundee, 1959). Instances of convulsions following intrathecal administration of gallamine in man are available to us (Mesry and Baradaran, 1974, Attygalle, G. M., Dundee, J. W., Gnanasunderam, R., personal communications).

CASE REPORT

A 48-year-old male weighing 60 kg was admitted to the General Hospital, Kurunegala, for inguinal herniotomy and repair. His medical history and examination revealed no abnormality and it was decided to give him a spinal anaesthetic, the usual procedure for such operations in Sri Lanka. Premedication was with papaveretum 20 mg i.m., 1 hr before operation. Packs containing all items necessary for the lumbar puncture, including ampoules of cinchocaine, are routinely autoclaved at 135°C for 5 min. Lumbar puncture was performed with the patient seated on the operating table. A Howard Jones needle was introduced at the lumbar 3/4 level without any difficulty and, after a free flow of c.s.f. was established, 1.5 ml of a solution (which was later identified as a solution of gallamine) was injected into the subarachnoid space. At this stage the patient did not complain of any pain or discomfort. He was then placed flat with a pillow under his shoulders and head. Usually, this technique gives a level of analgesia up to T 8. However, no attempt was made to assess the level of analgesia in this case and the operation was allowed to commence after the usual period of about 10 min of the intrathecal injection.

As the incision was made, the patient complained of intense pain and it was apparent that there was no analgesia. The patient was now treated as a case of “failed spinal” and a general anaesthetic was administered. Thiopentone sodium 400 mg with atropine 0.6 mg was administered i.v., followed by suxamethonium chloride 60 mg for oral endotracheal intubation. Anaesthesia was maintained with nitrous oxide and oxygen in a closed circuit with intermittent i.v. injections of suxamethonium. Halothane 1% was given intermittently. The surgical procedure was completed uneventfully and the patient returned to the ward after a stay of about 10 min in the recovery area, nothing abnormal having been noticed.

About 1 hr 45 min after the intrathecal injection the patient had unusual muscle spasms, initially confined to the lower limbs. These spasms were non-purposive. They were not prolonged; complete relaxation followed each contraction. The patient became anxious as violent incoordinate thrashing movements of the legs, quite unlike those that could be attributed to the recovery phase of general anaesthesia or to the toxic reactions of a local anaesthetic drug, appeared. There was no change in the arterial pressure at this stage, although the pulse rate had increased from 72 to 100 beats/min. Intramuscular promethazine 50 mg was followed by pethidine 50 mg i.v. This allayed the patient's anxiety, but did not in any way decrease the frequency or severity of the incoordinate contractions.

Three hours after the intrathecal injection, the
arterial pressure had increased to 170/110 mm Hg from the value of 140/90 mm Hg recorded before operation, and the pulse rate had increased to 110 beats/min. The patient was pyrexial (41.7°C), and was sweating profusely. There was no cyanosis. It became apparent that the drug injected intrathecally could not have been cinchocaine. Unfortunately, the used ampoule had been discarded.

In spite of the administration of promethazine and pethidine, the contractions continued and were increased in severity by sensory stimuli. Touching of the lower limb or allowing the breeze from a fan to play on the patient’s body triggered a muscle spasm. There was intense hyperaesthesia. The patient was placed in a darkened room and left undisturbed. Diazepam (Valium) 10 mg and hydrocortisone 100 mg were given i.v., together with 500 ml each of 5% dextrose and 0.9% saline. At this stage there were sufficient grounds to suspect that the drug administered intrathecally could have been gallamine. We had knowledge of the effects observed on previous accidental injection of gallamine intrathecally and further, there was a strong similarity between the ampoules containing gallamine and those containing cinchocaine. A lumbar puncture was performed and 15 ml of c.s.f. was withdrawn, almost 4 hr after the onset of the spasms. The c.s.f. was clear and not under tension; the specimen was sent for analysis.

During the next hour the contractions became less frequent, but the level of segmental involvement had reached the trunk muscles. Seven hours after the intrathecal injection the patient lost consciousness and had pin-point pupils. His arterial pressure was now 180/110 mm Hg, and the pulse rate was 130 beats/min and regular. Pulmonary ventilation was adequate on clinical assessment and there was no cyanosis. Dexamethazone (for the treatment of possible cerebral oedema) was given i.v. followed by diazepam 5 mg i.v. as necessary (a total dose of 50 mg diazepam was given). On the following morning the spasms were less intense and less frequent. The patient was conscious but disoriented; the pupils were still constricted. Weakness of the lower limbs and hyperaesthesia of the lower limbs and trunk were still present, although reduced.

The arterial pressure was 140/100 mm Hg and the pulse rate was 72 beats/min. The patient continued to improve and was allowed out of bed at 72 hr after the operation. At this time he had tenderness of the calf muscles. He was discharged from hospital on the 10th day after operation in good condition. The c.s.f. was analysed for the presence of gallamine by thin layer chromatography and ultra violet spectrophotometry.

**METHOD OF ANALYSIS**

Gallamine triethiodide inj. B.P. 4% (w/v) solution and cinchocaine hydrochloride heavy spinal solution 1:200 in 6% dextrose were used as standards, and c.s.f. from a healthy male subject was used as a control. The chromatographic plates for thin layer were of glass (20 cm x 20 cm) with Kieselgehr G (Nach Stahl) as the adsorbent. The plates were prepared as described by Sentheshanmugenathan, Rodrigo and Kamalanathan (1969). Standard solutions of gallamine and cinchocaine and c.s.f. were applied using a 10-μ litre pipette. The plates were irrigated for about 75 min using n-butanol/acetic acid/water (4:1:5 by volume, upper phase). During this period the solvent front moved about 10 cm from the starting line. The plates were dried and, when viewed under ultra violet light, cinchocaine appeared as a light blue fluorescent spot while gallamine did not show fluorescence. The plates were then sprayed with ninhydrin and dried at 120°C for 10 min. Gallamine appeared as a reddish spot on a white background, while there was no colouration with cinchocaine.

In addition the presence of gallamine and cinchocaine in the c.s.f. were identified by studying their absorption curves over the range 200-400 μ using a Unicam SP-600 recording spectrophotometer. Measurements were made against a blank containing only water.

**Isolation of gallamine from c.s.f.**

Gallamine and cinchocaine are both readily soluble in water and ethanol. This was made use of to isolate gallamine from the c.s.f. and to obtain it in a reasonably pure and concentrated form. 10 ml of c.s.f. from the patient (c.s.f. test) and from a “normal” person (c.s.f. control) were first evaporated to dryness under reduced pressure in a rotatory evaporator mix and extracted with ethanol and re-evaporated. The dry residual mass thus obtained was dissolved in distilled water and used for identification.

**RESULTS**

The chromatogram obtained with gallamine (G), cinchocaine (N), c.s.f. test (T), c.s.f. control (C), c.s.f. control with gallamine (CG), c.s.f. control with cinchocaine (CN), c.s.f. control with gallamine and cinchocaine (CGN) and gallamine with cinchocaine (GN), is shown in figure 1. When the plate was viewed under ultra violet light, the light fluorescent spot corresponding to cinchocaine was seen wherever...
ACCIDENTAL SUBARACHNOID INJECTION OF GALLAMINE

FIG. 1. Thin layer chromatogram on silica gel using n-butanol/acetic acid/water (4:1:5) after spraying with ninhydrin. Obtained with gallamine (G), cinchocaine (N), gallamine and cinchocaine (GN), c.s.f. control (C), c.s.f. control with gallamine (CG), c.s.f. control and cinchocaine (CN), c.s.f. control with gallamine and cinchocaine (CGN) and c.s.f. test (T).

Cinchocaine occurred. It was not seen in the c.s.f. test and c.s.f. control.

On spraying with ninhydrin and drying at 120°C, the red spot corresponding to gallamine was present in those solutions containing gallamine. The c.s.f. test also showed a red spot corresponding to gallamine, while the c.s.f. control did not. In addition, all c.s.f. samples gave another ninhydrin-positive spot with an RF different to that of gallamine. These may be a result of the presence of amino compounds in the c.s.f.

These results were confirmed by U.V. spectrophotometry. The ultra violet spectrum of gallamine, cinchocaine, and c.s.f. control gave the maxima as shown in table I.

The c.s.f. test gave the characteristic maxima of gallamine at 225 m\(\mu\). The peak at 270 m\(\mu\) was broad and flat. This is probably a composite peak as a result of gallamine peaks at 267 m\(\mu\) and 275 m\(\mu\), together with the peak from c.s.f. at 270 m\(\mu\). There was no peak in the c.s.f. test corresponding to cinchocaine. These tests, therefore, clearly indicated that gallamine and not cinchocaine was present in the c.s.f. of the patient.

**DISCUSSION**

Drugs which are fully ionized and which are not lipid soluble do not cross the blood-brain barrier in appreciable amounts (Goodman and Gilman, 1970a). Gallamine triethiodide, which has a \(pK_A\) of between 13 and 14 (Wylie and Churchill-Davidson, 1972) is fully ionized at the normal body pH and is not lipid soluble. Thus it would not be expected to cross the blood-brain barrier when clinical doses are used for muscle relaxation. This has been confirmed in dogs by Dal Santo (1972). On the other hand, quaternary neuromuscular blocking agents when applied by micro-iontophoresis exhibit blockage at various sites in the c.n.s. (Goodman and Gilman, 1970b; Wyke, 1959a,b). Tubocurarine and gallamine, which are quaternary compounds, are the commonest long acting relaxants in use in anaesthesia today. It has been shown (Salama and Wright, 1950) that, in the cat, tubocurarine injected intraventricularly, intracisternally and intrathecaly produces convulsions. On the other hand, the intraventricular injection of gallamine in cats produces c.n.s. effects which are milder and more restricted in distribution than those observed with tubocurarine (Salama and Wright, 1952). Intraventricular gallamine caused spontaneous movements of the head and fore-limbs and the trunk and respiratory muscles, but not the muscles of the lower limbs. The contractions were never generalized and were not seen in all the experimental animals. In these experiments, convulsions did not occur after the intrathecal injection of gallamine.

It is apparent that these effects of intrathecal gallamine in cats are different from what we have observed in our patient. Marked motor activity was seen in the case reported here and in those cases whose reports are available as personal communications. In one of the latter (Dundee, J. W., personal communication) the final outcome was not known*; the two patients who received intrathecal gallamine died after convulsions developed "soon after the injection"; no information is available on the latency of onset. In contrast, in our patient, about one-and-a-half hours

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**TABLE I. U.V. absorption maxima of gallamine, cinchocaine, c.s.f. test and c.s.f. control.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Wavelength (m(\mu))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallamine</td>
<td>226</td>
</tr>
<tr>
<td>(Flaxedil)</td>
<td></td>
</tr>
<tr>
<td>Cinchocaine</td>
<td>230 246</td>
</tr>
<tr>
<td>(Nupercaine)</td>
<td></td>
</tr>
<tr>
<td>C.s.f. test</td>
<td>225</td>
</tr>
<tr>
<td>C.s.f. control</td>
<td>270</td>
</tr>
</tbody>
</table>

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*A period of convulsions was followed by paralysis, but the trachia was intubated, the lungs were inflated, and the patient suffered no ill effects.*
The changes in arterial pressure were similar to those observed in cats after intraventricular and intrathecal administration of tubocurarine and intraventricular administration of gallamine (Salama and Wright, 1950, 1952). In the latter studies no mention is made of any changes in pulse rate and temperature.

In cats, full dilatation of the pupils has been observed after the intraventricular injection of tubocurarine. Sometimes, however, initial dilatation of the pupils was not maintained, but the pupils alternately contracted and dilated about once every minute, after which full steady dilatation persisted. No pupillary changes were noticed after intrathecal injection of tubocurarine or gallamine in cats (Salama and Wright, 1950, 1952). Our patient, in contrast, showed pupillary constriction.

Another observation which we cannot explain is the absence of any change of respiratory effort. In cats after intrathecal administration of tubocurarine, the respiratory muscles showed convulsive movements and the breathing became deeper and increased in rate. Similar changes did not occur in cats after intrathecal administration of gallamine (Salama and Wright, 1950, 1952).

Perhaps our patient survived because he was less sensitive than other patients who received intrathecal gallamine. In the experiments of Salama and Wright (1952) not all the animals who received gallamine developed contractions. The other explanation for the recovery of our patient may be the removal with the cerebrospinal fluid, although late, of a great proportion of the injected drug. The total amount of gallamine removed in the c.s.f. was not estimated. Whatever amounts of drug remained would have been removed from the c.s.f. by way of the lymphatics and veins in addition to its removal by the arachnoid granulations (Wyke, 1959a,b). It is known that the removal of gallamine from the c.s.f. when injected intraceresternally or intrathecally is rapid; further, in dogs, gallamine is expelled from the subarachnoid space unchanged (Dal Santo, 1972).

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REFERENCES


faire entreprendre le traitement le plus rapidement possible, car la drogue peut encore être identifiée dans le fluide cérébro-spinal 90 minutes plus tard. L'enlèvement du fluide cérébro-spinal et la sédation aurait probablement pu éviter une issue fatale à notre malade.

INJECCION ACCIDENTAL DE GALAMINA POR DEBAJO DE LA ARACNOIDES

SUMARIO
Se han registrado casos de inyección accidental de galamina por debajo de la aracnoides, y su tratamiento. Se describen los métodos de identificación de la medicina en el fluido cerebro-espinal. Debe iniciarse el tratamiento en una fase precoz, ya que la medicina todavía era identificable en el fluido cerebro-espinal después de 90 min. La extracción del fluido cerebro-espinal y la aplicación de sedantes pueden haber impedido unas consecuencias fatales en nuestro paciente.