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Widespread Hyoscine Hydrobromide Toxicity Due to Contract Manufacturer Malpractice

The Travacalm Episode

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Abstract

An outbreak of hyoscine hydrobromide toxicity was detected through the Australian pharmacovigilance system. The unexpectedly wide variation in hyoscine hydrobromide content between individual tablets within single packets created difficulties in initially explaining the clinical experiences. Strict time requirements for review of incoming adverse drug reaction reports and close involvement of the highly skilled national drug regulatory laboratory resulted in early identification of the cause of the outbreak and led in turn to the identification of malpractice by the contract manufacturer.

In a 7-day period (10 January 2003–16 January 2003), six local reports of suspected adverse reactions to a product sold to prevent and treat travel sickness (Travacalm® Original [1], Key Pharmaceuticals, Rhodes, NSW, Australia) were received by the Australian Adverse Drug Reactions Unit (ADRU) of the Therapeutic Goods Administration (TGA). Each tablet was stated to contain dimenhydrinate 50mg, hyoscine hydrobromide 0.2mg and caffeine 20mg.

The reports related to patients located in three states of Australia. Four patients were adults (age range 40–60 years; two male, two female) and two were male children aged 6 and 9 years. Two reports were sent to the TGA by general practitioners, two by a pharmacist and one by a relative of a patient. The sixth report was made by a relative of a patient to the sponsor company (Key Pharmaceuticals), which provided it to the TGA.

1. Case Details

1.1 Adults

The onset of symptoms occurred about 1 hour after ingestion of one tablet in one adult patient and after ingestion of two tablets in a second adult patient. The other two adult patients each took one

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tablet uneventfully followed by two tablets about 7 hours later and the onset of symptoms was during the same day but was not more specifically reported. The reports described a number of symptoms and signs as shown in table I. Two of the patients had treatment in the Accident and Emergency Departments of hospitals, where treatment included intravenous fluids and in one case a cerebral computed tomography scan and a third was given intravenous sedation by a general practitioner. Two patients had recovered within about 24 hours, whereas the other two had some residual symptoms about 2 days after the onset. Batch 78586 (expiry date 08/2005) was identified as the ingested product in one case and the likely batch in two other cases.

1.2 Children

The reactions in the two children were characterised by hallucinations and agitation. In one child, they were described as "vivid visual and auditory hallucinations with mild agitation, pressure of speech and insomnia", whereas the other child became disoriented and hallucinated and subsequently became very agitated. The doses taken were half a tablet by the younger boy and one tablet "dissolved in teaspoon of peanut butter" in the other boy. Times from ingestion to onset of symptoms were 1 hour and about 4.5 hours, respectively. One child was observed in hospital overnight. Both recovered from the reaction.

Table I. Reactions in adult patients[a]

Reaction descriptions	Number of patients
Abnormal behaviour or confusion or disorientation	3
Hallucinations or visual hallucinations	3
Agitation or anxiety	2
Dizziness or abnormal gait	2
Dysarthria or garbled speech	2
Fatigue	2
Blurred vision	1
Dry mouth	1
Upset stomach	1
Muscular weakness	1
Amnesia	1
Urinary retention	1

a Reaction terms included in adverse reaction reports relating to four adult patients.

The younger child had taken an identical dose of Travacalm® 2 weeks previously without ill effect and had also a single dose of Donnalix® Elixir 4 days previously without ill effects. This product was probably Donnalix® Oral Liquid (AUST R 13872, Wyeth Consumer Healthcare, Baulkham Hills, NSW, Australia), which contains hyoscyamine sulfate 20.74 μg/mL, atropine 3.88 μg/mL and hyoscine hydrobromide 1.3 μg/mL.

The other child had taken half a Travacalm® tablet about 2 years previously without ill effects. Follow up by the product sponsor and ADRU implicated the same batch (78586; expiry 08/2005) in both cases.

2. Investigations and Outcome

On 16 January 2003, staff of the TGA discussed the reports out of session with two clinicians who were members of the Medicines Evaluation Committee, which advises the TGA about over-the-counter (OTC) medicines. They advised that the reactions were consistent with hyoscine poisoning and that the batch should be withdrawn. However, there was no ready explanation why some of the patients had experienced the effects on one exposure but not on an earlier exposure. Three recent batches of Travacalm® products had been made by a different contract manufacturer (Pan Pharmaceuticals) to that used previously. The sponsor had been advised that testing of these batches had shown that the content of each active ingredient was within specifications and in particular that Pan Pharmaceuticals' batch-release certificates showed compliance with the requirement for uniformity of content of the hyoscine hydrobromide content.

Over the weekend of 18 and 19 January 2003, staff of the TGA Laboratories conducted testing of individual tablets from samples of the suspect batch 78586 provided by Key Pharmaceuticals and purchased by the TGA from a pharmacy. By the afternoon of 20 January 2003, the Laboratories had found that the hyoscine hydrobromide content of individual tablets from these samples ranged from

'not detected' to 164% of the label claim. This information was contrary to the information from the contract manufacturer and provided an explanation as to why reactions had been experienced on some, but not all, occasions. On 21 January 2003, Key Pharmaceuticals commenced a national recall of the three batches of Travacalm® Original that had been made by Pan Pharmaceuticals. More extensive testing of these three batches showed even greater variation in content of hyoscine hydrobromide between individual tablets from batch 78586 and less marked but unacceptable variation in the other two batches (table II). The sponsor later recalled two batches (79376; 77163) of another product manufactured by Pan Pharmaceuticals (Travacalm® HO; hyoscine hydrobromide 0.3mg) after identifying that they too did not comply with the specification for uniformity of content. Pan is believed to have used an unvalidated mixing procedure in the preparation of these products.

Investigations by the TGA found that records at Pan Pharmaceuticals showed that the batches of Travacalm® Original had passed the test for uniformity of content of hyoscine hydrobromide when this was not the case. Subsequent investigations by the TGA found multiple failures to observe Good Manufacturing Practice and resulted in the recall of >1200 products made by Pan. In relation to Travacalm®, Pan Pharmaceuticals and an employee have since been convicted of multiple charges under the Therapeutic Goods Act 1989 of manufacture of a counterfeit medicine and under the New South Wales Crimes Act 1900 of causing grievous bodily harm by negligent act.

Table II. Hyoscine content of individual tablets[a]

Batch and expiry date	Number and source of tablets tested	Lowest value (% of label claim)	Highest value (% of label claim)
77164; 06/2005	Three tablets from each of two packets and two tablets from each of two packets. Total = 10 tablets	68.1	120.6
78586; 08/2005	Five tablets from each of six packets. Total = 30 tablets	Not detected	707.3
79954; 10/2005	Two tablets from each of four packets and one tablet from each of two packets. Total = 10 tablets	3.6	123.9

a Results of analysis by Therapeutic Goods Administration Laboratories of hyoscine hydrobromide content of individual tablets sampled from three batches of Travacalm® Original tablets (see section 2). The product had a 2-year shelf life.

Following the recall, reporting of suspected reactions to Travacalm® products was stimulated greatly. By September 2004, the ADRU received an additional 179 reports of suspected adverse reactions to Travacalm® Original, Travacalm® HO or otherwise unspecified Travacalm® products. These included a further 74 reports specifically implicating Travacalm® Original batch 78586 and 30 specifically implicating batch 77164. The majority of these reports described symptoms similar to those described in table I. There were no deaths reported in the 179 reports, but 26 included explicit mention of treatment at a hospital. Supply of both products has resumed in Australia, following a change of contract manufacturer.

3. Discussion

Hyoscine hydrobromide, or scopolamine hydrobromide, is a very old drug and much of the available knowledge is in the form of case reports. In studies of oral doses ≤0.6mg, the adverse effects were usually limited to dry mouth, blurred vision and mydriasis.[1-3] Hallucinations and other severe adverse CNS effects have been reported with higher oral doses when used in psychiatric practice,[4] taken as an overdose of a medicine[5,6] or as an adulterant to drinks.[7-9] The symptoms reported with the batches of Travacalm® Original are consistent with excessive doses of hyoscine.

We believe that such wide-scale poisoning with hyoscine hydrobromide as a consequence of incorrect manufacturing of a medicine has not been described previously. The Australian adverse reaction reporting scheme was established in 1964 in the wake of the thalidomide events with the intention of detecting adverse reactions to properly manufactured medicines. From time to time, reports are received about possible faults in medicines. For example, in 1983, three Australian reports describing hypotension following injection led to the inter-

national recall of a batch of salmon calcitonin injection (Calsynar® injection, batch GA5006, Armour Pharmaceutical Co Ltd, UK).[10] The National Biological Standards Laboratory (as the TGA Laboratories were then known) demonstrated that infusions of this batch, but not other batches, caused hypotension in anaesthetised rats and contained significant amounts of a foreign substance. It emerged that the batch contained sodium azide instead of sodium acetete as a consequence of a dispensing error during manufacture (unpublished data). A small increase in Australian reporting of hypotensive reactions to a brand of polygeline solution (Haemaccel®, Roussel) in 1998 contributed to the initiation of investigations, which linked the adverse effect to a change in the method of manufacture (unpublished data). In all, 170 batches of the product were recalled worldwide.[11]

Three factors contributed to the prompt recognition of the problem with Travacalm®. First, five of the events were reported directly and promptly to the national centre by the doctors and pharmacist. Second, early identification of a possible problem followed prompt clinical review of incoming reports at ADRU in compliance with an in-house performance requirement. Third, access to advice and rapid analysis by an internationally recognised laboratory for testing medicines gave a prompt explanation for the clinical observations.

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