How the Bindeez were busted

It's slightly ironic that, having spent your career as a biochemical geneticist, you make your name in toxicology, but that is exactly what has happened to Kevin Carpenter. He told Kate McDonald how he tracked down the 'blip' in the Bindeez beads.

When a two-year-old child presented at the Children's Hospital at Westmead in Sydney last year with a decreased level of consciousness, no one was quite sure what was wrong with him.

He had spent the morning playing in the backyard with his siblings and appeared to be fine. Suddenly, however, he began walking with a staggered gait, as if drunk, and fell into a deep sleep from which he was difficult to rouse. Seven hours after he presented, he was back to normal.

As is normal practice for a child with a reduced level of consciousness, a full range of tests were conducted, including toxicology screens, which were all normal.

The emergency doctors then considered the possibility of a metabolic disorder, because in children this can happen very quickly. To rule this out, they ordered a urine metabolic screen, which is where Dr Kevin Carpenter came in.

Carpenter trained initially in chemical pathology in his native UK and then specialised in paediatric chemical pathology, which led to the study of inborn errors of metabolism. He is one of a small community of inborn error specialists in Australia and is now principal scientist at the NSW Biochemical Genetics Service at Westmead.

The urine metabolic screen, which includes organic acid testing, came back positive for gamma-hydroxybutyrate (GHB). Although GHB is best known as a recreational drug, it is also a naturally occurring substance in the body. It is excreted in a certain inborn error called succinic semialdehyde dehydrogenase (SSADH) deficiency, also known as gamma-hydroxybutyric aciduria. SSADH is an enzyme whose job is to convert succinic semialdehyde into GHB, which acts as a neurotransmitter and is a metabolite of gamma-aminobutyric acid (GABA).

If you have an SSADH deficiency, GHB levels build up, which is seen in the urine, Carpenter says. 'But as well as seeing GHB in the urine of the patients who have the inborn error, you see another compound as well – 4,5-dihydroxyhexanoate lactone – and that wasn't there. I looked at the clinical information on request and I thought it was unusual with a child of this age, with this presentation, that it would be that particular inborn error.'

This is where the real sleuthing began. If the raised levels of GHB in the child's urine were not due to an inherited disorder then ingestion was the obvious suspicion. The child was still in hospital because he had picked up an infection, so another urine sample was taken and the GHB was absent.

Bindeez suspected

'At this point, the suspicion initially was that perhaps there was some GHB in the family somewhere, someone using it as a recreational drug and he'd got hold of it somehow', Carpenter says.

The child's mother denied the family had anything of the sort in the house, but she did mention that the child had eaten a substantial amount of Bindeez beads, a toy that involved creating pictures from little coloured beads that was named last year's Toy of the Year by the Australian Toy Association. Beads had been found in the child's vomit and in a stool sample.

'Very astutely, the doctor, Olivia Chan, said perhaps it was something on the beads', Carpenter says. 'She got hold of some of the beads that he'd been playing with and sent them to me and asked if I'd have a look for GHB.

'We had a look to see if there was anything there and there wasn't, but I did see a big peak on the chromatograph, which was something I hadn't seen before.'

Using a gas chromatography–mass spectrometry (GC–MS) instrument, Carpenter investigated the molecular weight of the chemical causing the peak. He then went to the literature to look for precursors of GHB.

Kevin Carpenter and a Bindeez sample. (Photo courtesy Agilent Technologies)

'The second one I came up with was 1,4-butanediol. I was very suspicious of what I was actually dealing with – I wanted to be sure it wasn't something that was just in that particular batch of beads.

'So I went and bought some more beads ... and put them through our system and found the same thing. Now I was sure that what was coming off the beads was consistent and I was pretty sure it was 1,4-butanediol, but I was not so sure that I was going to ask them to withdraw the Toy of the Year. I was fairly cautious about that.'

He then contacted the distributor of the toy in Australia, who put him in touch with the manufacturer, who provided him with a list of ingredients in the beads.

1,4-butanediol wasn't in there, but another chemical, 1,5-pentanediol, was. Still sure it was the former he was looking at due to the difference in molecular weights, he ordered a batch of 1,4-butanediol from laboratory chemical company Sigma (delicately explaining to the sales person that he did not want to use it as a date-rape drug), ran it through the GC–MS and got the same peak.

Bindeez busted

In the meantime, the NSW Poisons Information Centre, also based at Westmead, had been informed, as had the Department of Fair Trading, which regulates potentially dangerous consumer goods in NSW.

Then another case turned up, this time a 10-year-old girl, with the same presentation. A urine sample was taken, the same chemical was confirmed, more beads were discovered, the department was informed and by the next day Bindeez were being taken from the shelves.

Curiosity still sparked, Carpenter spent a bit of time having a look at 1,4-butanediol and what it could possibly be used for in the chemical industry.

'One of the things that I found was that it could be used as what they call a sizing agent - when it is mixed with water-soluble glue it stops the beads from getting tacky in a humid atmosphere. So I thought, "Here's a good reason to use 1,4-butanediol, which has similar properties to 1,5-pentanediol."

'The story was that 1,5-pentanediol was in the list of ingredients that the manufacturer supplied, and as far as the distributor knew, that was what was in them. But it was actually 1,4-butanediol - it subsequently came to light that the factory that was producing the toy had switched from 1,5-pentanediol to 1,4-butanediol without telling anyone.

'There are a couple of theories as to why they might have done that: one reason is that butanediol is about a third of the price of pentanediol and the other is that apparently it makes the beads easier to mould. The original formulation ... didn't contain this chemical.'

Further investigation took Carpenter into the world of GHB, both as a naturally occurring substance and as a popular recreational drug. '1,4-butanediol is initially metabolised by alcohol dehydrogenase, the enzyme in your body that normally gets rid of alcohol', he says.

'This acts on 1,4-butanediol and converts it to an intermediate that is then acted upon by aldehyde dehydrogenase, and then forms GHB. It's two normally occurring enzymes in the body that are effectively going through a process that would detoxify the normal alcohol, but in the case of this particular diol, the end product is a neurotransmitter. The chemistry has been known for a long time.

'When GHB first came on the scene, it was used as an anaesthetic drug. It was known to be present as a neurotransmitter in the brain, then it was found to be an anaesthetic drug, and then it was withdrawn because of the problems of using it in a controlled manner.

'It became quite popular as a drug of abuse and was then classed as a schedule 1 drug by the US Food and Drug Administration. Pretty much immediately that happened, people realised that if you used 1,4-butanediol instead, which isn't a banned drug, it would convert to GHB and you'd get the same effect. If you do an internet search of 1,4-butanediol the vast majority of things that will come up will be about how to get a high off it.'

No high here

Interestingly, the fact that 1,4-butanediol is metabolised by alcohol dehydrogenase and aldehyde dehydrogenase might mean that those people who are unable to metabolise alcohol due to common polymorphisms, particularly people from eastern Asia, would not metabolise 1,4-butanediol in the same way. This turned out to be the case.

'There was a study done where they wanted to look at the effect of giving 1,4-butanediol and how much of it was converted to GHB', Carpenter says. 'They found that the vast majority of people almost immediately converted it completely to GHB.

'The only exceptions are people who have the polymorphisms in alcohol dehydrogenase - if you are one of those people who can't metabolise alcohol you wouldn't get much of a kick out of GHB.'

The case made headlines around the world and makes for a fascinating story. The speed with which those involved acted was outstanding - just over a week between the first child presenting and the product being recalled - and it was a marvellous piece of detective work. Carpenter happily says nothing like it had ever happened to him before.

'You work for 35 years in genetics and the thing that makes your name is toxicology', he says. 'I didn't think I was going to find something in this case but I'm pleased I did.'

Kate McDonald is editor of *Australian Life Scientist*.
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