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Acute anticholinergic poisoning in children

兒童急性抗膽鹼中毒

We report two cases of unintentional poisoning with anticholinergic agents. The first patient, a 7-year-old girl, was prescribed four different medications by a general practitioner for treatment of abdominal colic and diarrhoea. All drugs had anticholinergic properties. The second patient, a 16-month-old boy, ingested his mother's cyproheptadine tablets. Both children presented with central and peripheral symptoms and signs compatible with acute anticholinergic syndrome. They recovered spontaneously following intravenous fluid replacement and close observation. Gastric lavage was also performed on the boy. Poisoning with cholinergic antagonists in children is a potentially serious hazard in Hong Kong. It may be avoided by careful prescribing on the part of general practitioners and safe storage of all medicinal products in the home environment.

本文報告兩個抗膽鹼藥物意外中毒的病例。第一個病例是一位7歲女童，由全科醫生處方四種藥物治療腹絞痛和腹瀉。所有藥物均含有抗膽鹼成份。第二個病例是一位16個月大的男嬰，誤吞母親的賽庚啶片。兩人都出現與抗膽鹼綜合症吻合的中樞抗膽鹼綜合徵及週邊抗膽鹼綜合徵。經過靜脈液體補充注射和嚴密觀察，而男嬰亦接受了洗胃後，兩人很快康復。在香港，兒童有可能因為膽鹼拮抗劑中毒而受到嚴重傷害。醫生謹慎處方，在家居環境小心擺放藥物，都能避免類似的藥物中毒。

Key words:
Cholinergic antagonists;
Cyproheptadine;
Drug toxicity;
Lomotil;
Scopolamine derivatives

關鍵詞：
擬膽鹼拮抗劑；
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Introduction

Systemic use of anticholinergic agents is seldom indicated in children. Their use as antimotility agents has little scientific basis. Other medications commonly used in children may possess non-therapeutic anticholinergic properties. Inadvertent drug combination, variability in pharmacokinetics, or accidental ingestion of these compounds may lead to acute intoxication, a condition also known as anticholinergic syndrome. The following cases illustrate this potentially life-threatening complication.

Case reports

Case 1

A 7-year-old girl was admitted with a 4-day history of vomiting and abdominal pain. She also complained of fever, sore throat, runny nose, vomiting, and the passage of loose bowel motions on two occasions. She had enjoyed good health prior to this illness. On the second day of symptoms, she visited her general practitioner. There was no improvement in symptoms by day 4 when she returned to the same doctor and was given a new prescription. At this time her bowel movement had stopped but abdominal pain, vomiting, and poor appetite persisted. On

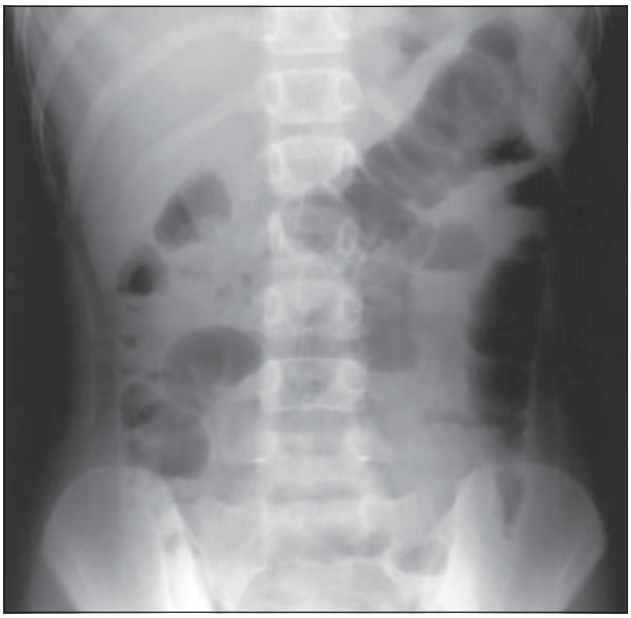

Fig. Erect abdominal radiograph showing dilated bowels with multiple air-fluid levels

admission, a provisional diagnosis was made of acute gastroenteritis. The child was drowsy on admission, but easily roused and could speak coherently. Her tympanic temperature was 37.9°C. There were mild tachycardia and tachypnoea, with rates of 120 beats per minute and 24 breaths per minute, respectively. Blood pressure was normal. Mucous membranes were dry. Both pupils were dilated, measuring 5 mm in diameter, but responsive to light. Neurological examination was otherwise unremarkable. Her abdomen appeared full but there was no tenderness and no organs were palpable. Bowel sounds were sluggish. Laboratory investigations revealed a mildly elevated serum creatinine level of 55 μmol/L (reference range, 35-53 μmol/L), normal serum electrolytes, amylase level, and blood cell counts. Abdominal X-ray revealed dilated small and large bowels with multiple air-fluid levels (Fig).

A review of the drug history revealed that the general practitioner had initially prescribed hyoscine methylbromide, loperamide, and dimethicone 40 mg 4 times a day. At the second visit, all medications were stopped and changed to hyoscine butylbromide, diphenoxylate-atropine, L-chlorpheniramine, and paracetamol 500 mg 4 times a day (Table[1]). Acute anticholinergic poisoning with mild dehydration and drug-induced ileus was diagnosed. Vital signs remained stable and her condition improved with intravenous hydration therapy. There was no urinary retention and she was discharged 36 hours later following complete recovery.

Case 2

A 16-month-old boy was found to have taken an unidentified amount of his mother's medication. Two hours later he presented to the hospital when he was noted to be irritable and felt "hot". Medical history was unremarkable and he was not on any other drug treatment. The medication was identified as 4-mg cyproheptadine tablets that the mother took as an appetite stimulant. The rectal temperature measured 37.8°C and there was mild tachycardia and tachypnoea, with resting rates of 160 beats per minute and 30 breaths per minute, respectively. Blood pressure and percutaneous oxygen saturation were normal. Pupils were dilated at 5 mm diameter bilaterally, and response to light was sluggish. Localising or lateralising neurological signs were absent. Abdominal examination was normal and the bladder was not palpable. Acute anticholinergic poisoning was diagnosed. Initial treatment consisted of gastric lavage and intravenous fluid replacement. The child's vital signs remained stable and feeding was resumed. There was no urinary retention. Complete blood count, blood urea nitrogen, and serum electrolytes were within normal limits. He was discharged the next day when all signs of toxicity had resolved. Advice was given with regard to safe storage of medication in the home.

Discussion

Anticholinergic agents act by blocking the action of acetylcholine on the postsynaptic muscarinic

Table. Drugs with anticholinergic/antimotility properties given in case 1

Medication (proprietary name)	Dosage		Recommended dosage[1]
	Actual	Adjusted for weight	
Hyoscine butylbromide (Buscopan)	10 mg qid*	-	10-20 mg 3-5 times/day for age >6 years
Hyoscine methylbromide (Holopon)	0.5 mg qid	0.06 mg/kg/day	0.2 mg/kg/day divided into 4 doses
Diphenoxylate-atropine (Lomotil)	2.5 mg qid	0.3 mg/kg/day	0.3-0.4 mg/kg/day divided into 4 doses; for age >2 years only
L-chlorpheniramine (Piriton)	4 mg qid	0.48 mg/kg/day	0.35 mg/kg/day divided into 3-4 doses
Loperamide	2 mg qid	-	2 mg 3 times/day for body weight >30 kg

* qid 4 times a day

receptors in the post-ganglionic nerve endings of the parasympathetic nervous system, and widespread areas of the central nervous system including the cortex, hippocampus, and the extrapyramidal system where acetylcholine functions as a neurotransmitter.[2] Systemic anticholinergic agents are indicated in the treatment of movement disorders associated with dysfunction of the extrapyramidal system, peptic ulcer disease, sweating disorders, and bladder dysfunction.[1] Few indications exist for their systemic use in children. Atropine is used during cardiopulmonary resuscitation for bradyarrhythmias. Hyoscine (scopolamine) diminishes gastric acid secretion and was first licensed for the treatment of peptic ulcer disease. It is now more often used for controlling abdominal cramps as a compound with methylbromide (Holopon) or butylbromide (Buscopan), although evidence of their efficacy is lacking.[3] Atropine combined with diphenoxylate (Lomotil) is an antidiarrhoeal agent. Its effectiveness in children is doubtful[4] and serious and fatal toxicity has been reported.[5] Anticholinergic compounds have recently been found useful in the treatment of drooling in children with pre-existing central nervous system disorders.[6]

Many drugs commonly prescribed for children possess anticholinergic properties in addition to their therapeutic action: the first-generation antihistamines such as chlorpheniramine and tricyclic antidepressants are well-known examples. Other plant extracts used therapeutically (eg belladonna) or at leisure as herbal drinks may also have anticholinergic actions.[7] Thus, children may be unintentionally exposed to anticholinergic toxicity.

Anticholinergic syndrome

Poisoning with anticholinergic substances produces a clinical syndrome characterised by central and/or peripheral symptoms.[8-10] Altered consciousness, irritation, or confusion predominate when the central nervous system is involved. Pupillary dilatation may be a clue to the central anticholinergic syndrome, although it may be masked by the concomitant use of opioid compounds.

Peripheral indications of anticholinergic poisoning include dry mouth, hyperthermia as a result of loss of sweating, tachycardia, constipation, and urinary retention.[10] A combination of anticholinergic agents, or other compounds with similar activity, may lead to more severe toxicity and symptoms such as paralytic ileus. Serious anticholinergic syndrome has been reported in adults who took an over-the-counter sleeping remedy that contained hyoscine and cyproheptadine,[11] and suicide has been described in a young adult who consumed alcohol and an unknown amount of cyproheptadine.[12] Children may be more susceptible to the adverse effects of anticholinergic agents even at so-called 'therapeutic' doses.[13]

Toxicity of diphenoxylate-atropine (Lomotil)

The mainstay of treatment for childhood gastroenteritis is maintenance of fluid and electrolyte balance.[12] Antibiotic treatment is only indicated in the presence of invasive or severe infective agents such as cholera or bacterial dysentery. Antimotility agents, including anticholinergic or opioid agents, are not recommended. Amelioration of bowel movements may mask fluid loss into the third space and thus dehydration results (case 1).

Diphenoxylate is a congener of pethidine (or meperidine), marketed as Lomotil for the treatment of diarrhoea.[14] The atropine component was added to prevent the addictive potential of the antidiarrhoeal preparation. Diphenoxylate-atropine appears to be a safe and useful treatment in adults, but serious toxicity, sometimes fatal, has been reported in children following accidental or therapeutic ingestion.[5,15] In addition to the anticholinergic syndrome from atropine, the opiate action of diphenoxylate may lead to drowsiness, coma, and respiratory depression.[15] The severity of poisoning does not correlate with the amount ingested.[15] Clinicians should be aware of the occurrence of delayed opioid toxicity in a small proportion of patients that may be related to delayed absorption and the metabolism of diphenoxylate to difenoxin, a metabolite that is 5 times more potent than the parent drug.[5]

Diphenoxylate-atropine has no place in the management of acute non-specific diarrhoea in children,[4] and deleterious effects are observed when it is used to manage antibiotic-associated diarrhoea.[16] Official warnings have been issued about the use of diphenoxylate-atropine in children and parents need to be given advice about the appropriate management of diarrhoea in children.[14] Antimotility agents should be avoided.

Management of anticholinergic syndrome

In a child with suspected anticholinergic syndrome, emergency hospital treatment should be instigated. Attempts should be made to empty the stomach, even when medical consultation is delayed, because of the antimotility property of anticholinergics.[17] In a symptomatic child with an adequate gag reflex, especially when a life-threatening ingestion is

suspected, an orogastric tube of the largest possible bore (16- to 28-French in children; 36-French in adolescents) should be used for gastric lavage.[17] Activated charcoal, 1 g/kg or 25 to 50 g in the older child, may be left in the stomach following gastric lavage.[10] Induced emesis is not advised, especially when there is altered consciousness. Intravenous fluid replacement is helpful when there are signs of dehydration, or if enteral feeding cannot be established. Close monitoring of the consciousness level, blood pressure, and heart rate is necessary. Urinary catheterization is indicated if there is urinary retention. Most patients will make a complete recovery when the ingested medication has been eliminated by the body. Toxicity from other ingested compounds, for instance, cardiac arrhythmias associated with antidepressant poisoning, and concomitant paracetamol toxicity must be looked for and treated accordingly. The narcotic effects of diphenoxylate may be reversed with an infusion of naloxone. Therapeutic or toxicological monitoring is generally not available. Nonetheless, care must be exercised in the interpretation of toxicological screening as false-positive results for tricyclic antidepressants have been observed in the presence of cyproheptadine intoxication.[18]

In the presence of serious or life-threatening complications, physostigmine given as a slow intravenous infusion may be tried.[11,19] Physostigmine acts as a cholinesterase inhibitor and prolongs the neurotransmitter activities of acetylcholine at the target tissues. As a tertiary amine, physostigmine is able to penetrate the blood-brain barrier and can reverse both central and peripheral anticholinergic symptoms. The recommended dose for young children is 0.02 mg/kg (up to 0.5 mg) per dose given as a short infusion over 5 minutes with cardiac monitoring.[10] Because of its short half-life, physostigmine infusion may be repeated every 5 minutes until a maximum dose of 2 mg is reached, or when cholinergic symptoms occur. Atropine must be available, at a dose half of the amount of physostigmine infused, if cholinergic toxicity is observed.

Conclusion

Anticholinergic syndrome is a potentially life-threatening complication associated with the use of drugs or herbal extracts that possess anticholinergic activity. Its occurrence in children may not be easily appreciated unless a high degree of suspicion is maintained. Antimotility agents are generally contra-indicated in the management of childhood gastroenteritis. Close monitoring and supportive care are usually adequate treatment for the anticholinergic syndrome. Physostigmine may be used as an antidote when there is serious toxicity. Judicious use of medicines with anticholinergic properties is recommended. The mandatory use of child-resistant caps on medicine containers elsewhere has significantly reduced the morbidity and mortality associated with accidental ingestion.[17]

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