Paediatric organophosphate poisoning – a rural hospital experience

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Objectives. To document the presentation and course of organophosphate poisoning (OPP) in children and to record the frequency of atropine toxicity during treatment.

Design. A retrospective observational study was conducted of all recorded paediatric cases of OPP admitted to a regional hospital over a 5-year period from 1 June 1996 to 31 May 2001.

Setting. The study was conducted at Eben Donges Hospital, a regional hospital in the Boland/Overberg area of the Western Cape, where pesticide-intensive fruit farming remains the largest revenue generator.

Subjects. The study included all children aged 12 years or less (as per health services classification) with confirmed OPP.

Results. There were 23 patients. Most of the cases came from the De Doorns area (35%), with poisoning by ingestion accounting for 61% of cases. A distinct seasonal predominance was found that coincided with the summer harvest. Mode of presentation was variable and was not related to the initial pseudocholinesterase level. Evidence of atropine toxicity occurred in 8 of the 18 cases treated with atropine. No statistically significant risk factor was found for atropine toxicity. The average duration of hospitalisation was 5.05 days, with 2 children requiring transfer to tertiary facilities.

Conclusions. The high number of referrals from a specific geographical area, combined with a 61% accidental ingestion rate, illustrates an area where legislation has failed to limit unnecessary exposure. Awareness of the seasonal predominance could prove pivotal to the success of future preventive strategies. Initial presentation and serum pseudocholinesterase levels did not correlate with duration of stay. The decision to transfer to a tertiary facility should only be explored once the patient has been stabilised with atropine. Atropine treatment is effective but carries a risk of toxicity. Glycopyrrolate may constitute an alternative treatment option.

S Afr Med J 2005; **95:** 678-681.

Eben Donges Hospital (EDH) is a regional hospital in the Boland/Overberg region of the Western Cape. It serves a diverse community whose economic stability is reliant on the intensive fruit-farming industry. This farming is heavily dependent on organophosphate (OP)-containing insecticides for pest control, often to the detriment of labourers' health. The combination of accessibility, limited legislation and lack of education has resulted in frequent OP exposure, including among children.

Acetylcholine, the neurotransmitter at postganglionic parasympathetic, preganglionic sympathetic and parasympathetic, somatic striated skeletal and central nervous system (CNS) receptors, is rapidly hydrolysed by an enzyme in the synaptic cleft, acetylcholinesterase.[1] OP compounds form covalent bonds with the latter resulting in an excess of acetylcholine, which produces hyperstimulation and the myriad of symptoms and signs characteristic of organophosphate poisoning (OPP).[2-6]

Anticholinergics, in particular atropine, have been the cornerstone of OPP treatment for decades.[7] Atropine's role as a competitive antagonist at the muscarinic receptors in the peripheral and CNS allows rapid control of the bradycardia, hypotension, bronchospasm, excessive secretions and gastrointestinal complications of OPP, allowing for stabilisation of the patient.[3] Atropine does not reverse the effects of OPP at the nicotinic and all CNS receptors and patients may require additional support for respiratory muscle paralysis/weakness and convulsions, etc.[3]

Atropine's biochemical structure allows it to pass through the blood-brain barrier, potentially reversing some of the CNS effects of the OPP; however it can also produce symptoms indistinguishable from the very condition the clinician is trying to treat, namely nervousness, drowsiness, mental confusion and agitation. These symptoms appear to be dose related and are a complication of treating OPP.[5]

Currently there is no literature documenting the incidence of CNS atropine toxicity in children during OPP treatment.

Objectives

The study aimed to document the presentation and course of OPP among children treated for this condition and to record the frequency of CNS atropine toxicity.

Method

A retrospective folder review was undertaken of all paediatric patients (age 12 years and younger) admitted to EDH with confirmed OPP over a 5-year period from 1 June 1996 to 31

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May 2001. The diagnosis of OPP was based on a combination of history of suspected poisoning, presenting symptoms and signs (Table I) and definitive confirmation using serum pseudocholinesterase levels. Participants' folders were reviewed for data on age, sex, geographical district/area of exposure to poison, presenting symptoms and signs, pseudocholinesterase level, mode of treatment, duration of hospital stay and documented evidence of CNS atropine toxicity. Atropine toxicity was defined as the persistence of symptoms of excessive nervousness, drowsiness, mental confusion, agitation or excitement after 24 hours in a child with dilated pupils and a clear record of repeated doses of atropine administration; once documented special investigations excluded mimicking conditions such as repoisoning with OP from fat stores and septicaemia. Folders with incomplete data and uncertain cases were excluded from the review.

This study has the potential to improve preventive strategies and community awareness of the OPP problem.

Statistical analysis

Categorical variables were compared using the Fisher's exact test, and groups were compared using the Mann-Whitney U-test. A level of significance of less than 0.05 was used throughout.

Results

During the study period 23 paediatric patients were treated for OPP at EDH. The demographics of these patients showed a male-to-female ratio of 12:11, with a median age of 4 years and a range of 1 - 12 years. Children from the De Doorns area in the Hexriver Valley accounted for 35% (N = 8) of poisonings, children from Worcester for 17% (N = 4), Breërivier and Robertson for 9% (N = 2) each respectively, and the remaining drainage areas had incidental cases. The documented sources of poisoning were as follows: 61% (N = 14) accidental ingestion of OPs, with unwashed freshly sprayed fruit or poorly marked storage containers as possible sources, 22% (N = 5) skin and inhalation exposure as a result of recent use of OPs for pest control in and around homes, and 17% (N = 4) unknown or unconfirmed source of poisoning. There appeared to be a definite seasonal predominance, with cases peaking between October and January, accounting for 70% (N = 16) of all cases (Fig. 1).

Table I. Symptoms and signs of organophosphate poisoning

Muscarinic effects
Cardiovascular system: bradycardia and hypotension
Gastrointestinal tract: salivation, nausea and vomiting, diarrhoea and abdominal pain, tenesmus and faecal incontinence
Respiratory system: bronchospasm, bronchorrhea
Eyes: miosis
Other: lacrimation, diaphoresis and urination
Nicotinic effects
Musculoskeletal: fasciculation, weakness, paralysis, cramps and respiratory paralysis
Cardiovascular system: tachycardia and hypertension
Central nervous system effects
Altered level of consciousness, agitation and confusion, delirium, coma, seizures, ataxia, dysarthria and respiratory depression

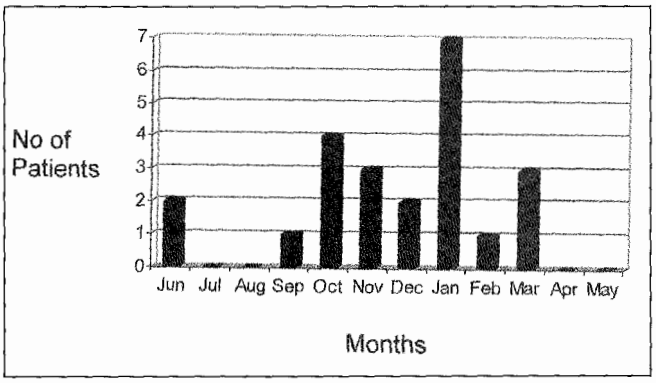

Fig. 1. Seasonal OPP incidence.

Presenting symptoms and signs were in keeping with those described by other authors, with abnormal pupils (78%) and excessive secretions (65%) the most common features (Table II).[7]

Table II. Summary of presenting symptoms and signs

	N (%)
Pin-point pupils	18 (78)
Excessive secretions	15 (65)
Decreased level of consciousness	9 (39)
Vomiting	9 (39)
Diarrhoea	7 (30)
Tachycardia	6 (26)
Confusion	6 (26)
Fasciculations	5 (22)
Respiratory failure	3 (13)
Apathy	3 (13)
Muscle weakness	2 (8)
Shock	2 (8)
Abdominal pain	2 (8)
'Garlic' odour	2 (8)
Irritability	1 (4)
Ingestion of poison	14 (61)
Skin and inhalation exposure	5 (22)
Unknown source of poisoning	4 (17)

All patients admitted were treated in the same way. Initial conservative therapy included gastric lavage and use of activated charcoal (for suspected ingestion cases), declothing and full-body wash, and cardiovascular and respiratory stabilisation. A single dose of obidoxime, a cholinesterase reactivator, was used in 9 cases on admission. Of the 23 cases, 20 received atropine (according to the recommended OPP dosage), 2 treated conservatively and 1 case received a glycopyrrolate (Robinul) infusion (Fig. 2).

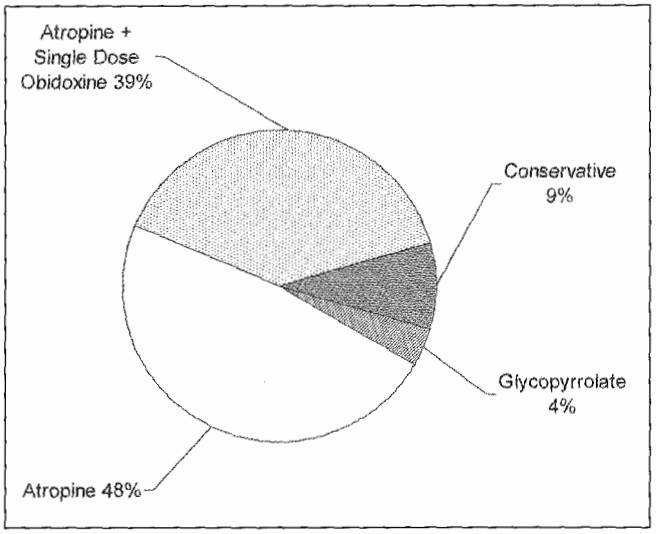

Fig. 2. Treatment summary.

Intubation was required in 4 children, of whom 2 received short-term (less than 24 hours) ventilation. The remaining 2 children were transferred to a tertiary facility, 1 for intractable seizures not controllable with conventional anticonvulsants and requiring a Thiopentone infusion, and the other for hypoxic cerebral damage from respiratory failure and cardiovascular collapse. The former child survived with neurological impairment and the latter died 10 days after presentation.

Documented evidence of CNS atropine toxicity occurred in 8 of the 18 cases (excluding the 2 transferred patients) treated with atropine, equivocating to 44% of cases. No statistically significant difference could be found when comparing patients with atropine toxicity and those without toxicity (Table III).

There was also no correlation between pseudocholinesterase levels and duration of stay, as shown in Fig 3.

Table III. Comparison of atropine toxicity groups (standard deviation)

Patient data	Atropine toxicity	No atropine toxicity
Age (yrs)	5.38 (3.623)	3.5 (2.415)
Duration of hospital stay (days)	4.82 (0.99)	4.9 (1.75)
Pseudocholin-esterase level (IU)	563.1 (285.6)	425.2 (401.8)
Ingestion of poison	5	4
Inhalation and skin exposure	2	3
Unknown source of poisoning	7	7

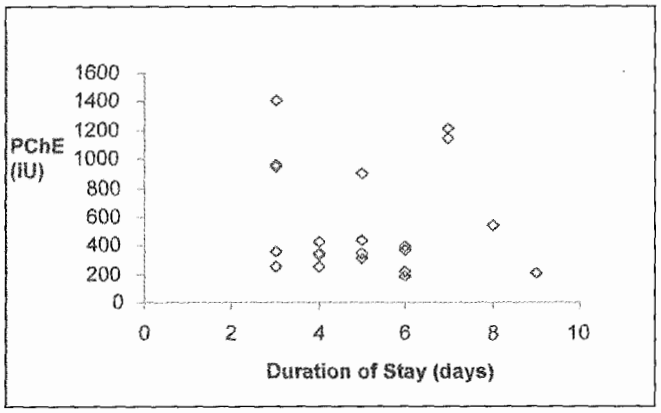

Fig. 3. Scatter plot of pseudocholinesterase level v. duration of stay.

Discussion

The liberal use of pesticides in the agriculturally rich region of the Western Cape has contributed significantly to the ever-increasing number of reported poisonings in this region. Pesticide poisoning in children under 14 years of age has a reported average incidence of 0.367/100 000. OPP accounts for 49.9% of all poisonings.[8] OPP is a notifiable disease in South Africa and it can be assumed that the reported numbers are a gross underestimation of the real problem.[9] Our study region is well represented in the above statistic.

The seasonal predominance between October and January is an overriding feature of these poisonings. The fact that incidence coincides with peak spraying activities (a trend also noted by other authors) could prove pivotal to the success of future preventive strategies.[10] OPP indicates a problem of increased exposure to and circulation of agricultural pesticides. More stringent enforcement of current legislation is required, along with a need for education. Education of both employees and employers cannot be overemphasised, as this remains pivotal in reducing exposure to these hazardous chemicals, especially among children. Legislation forcing farms to erect clear signage warning children and adults to keep away from recently sprayed areas may be an effective solution. School-based programmes (as attempted by the Department of Health a few years ago) and child-to-child programmes should be introduced. The high number of referrals from the De Doorns area (35%) in combination with 61% of poisonings by accidental ingestion indicates a high-risk area that would benefit from a structured education programme. Legislation, particularly in the De Doorns area, should be more strictly enforced, with seasonal air monitoring, more stringent control

interpreted as allowing children over 14 to consent independently to 'therapeutic' research.[7]

Researchers will now face new legal requirements that may affect recruitment and informed consent processes. Although the National Health Act[3] will not operate retrospectively, once it is implemented researchers may have to change current practices if they are not in line with the new provisions.

Aspects of the emerging ethical-legal framework are ambiguous and inconsistent

Key problems raised at the forum included:

1. The National Health Act[3] retains the contested distinction between 'therapeutic' and 'non-therapeutic' research in its provisions relating to research with children, despite the fact that most research contains interventions not intended to confer direct benefit to participants. It does not define either term.
2. It is not clear how the different phases of HIV vaccine trials would be classified in terms of the above distinction.
3. If HIV vaccine trials are classified as 'non-therapeutic' research (as early trials might be) the risk standard of 'not significant' risk must be met. There was some debate as to whether the above term introduced a more relaxed standard of risk for research involving children or alternatively whether it was substantively identical to current risk standards (routine tests or daily life). There was some debate as to whether the risks of HIV vaccine research (such as vaccine administration, risk assessments) could meet this standard set by the National Health Act.[3]
4. There are many inconsistencies between the National Health Act[3] and other critical pieces of legislation such as the Children's Bill.[4] For example, the National Health Act[3] requires dual consent for research from parents or legal guardians and where children are capable of understanding, children themselves.[8] This differs from the approach taken in the Children's Bill[4] which provides for independent consent by a child of a specified age and capacity (albeit in the case of medical treatment and operations and not research), which creates a wider category of persons who are able to act on a child's behalf,[9] and which requires that the views of a child be given due consideration bearing in mind the age, maturity and stage of development of the child.[10]
5. The National Health Act[3] requires 'therapeutic' research to be conducted only if it is in the 'best interests' of the child.[11] No guidance is provided in the Act on how one establishes what these 'best interests' are.
6. Both the National Health Act[3] and the Children's Bill[4] provide that in the event of an inconsistency their provisions will prevail.
7. Four ethical guidelines relevant to HIV vaccine research[5,6,12,13] offer some contradictory guidance regarding child participation on the following points: (*i*) the approach taken towards the analysis of risk and classification of research; (*ii*) the name given to risk levels allowed for child research, and the substance of the risk level allowed for child research; (*iii*) who has the authority to consent for child participation; and (*iv*) what risk parents or guardians are permitted to consent to on behalf of children when there is no direct benefit to the child and when there is a direct benefit.

It is the MRC's General Principles[6] that are most disjunctive with the other three increasingly well-harmonised guidelines.[5,12,13] As a result of these ambiguities and inconsistencies REC members reviewing trials and researchers planning trials may struggle to screen out 'unethical' or unlawful research practices involving child participants.

In some instances, the ethical-legal framework does not protect child welfare or promote critical research as effectively as possible

The following issues were discussed:

1. Section 71 of the National Health Act[3] purports to deal with the rights of children participating in research; however, it focuses on informed consent without considering other protections such as a child's right to privacy. As a result, there are many instances in which child research participants do not have explicit legal protection in South African law.
2. The National Health Act[3] creates additional procedural requirements that may burden investigators and RECs, e.g. when 'non-therapeutic' research is conducted on children then 'authorisation from the Minister' must be obtained.[14] Furthermore, the Minister is obliged to follow guidelines set down in the Act, in determining whether authorisation for non-therapeutic research should be approved. Concerns were raised regarding: (*i*) how this provision would operate in practice; (*ii*) whether it would delay research classified as 'non-therapeutic'; and (*iii*) how the Minister would interpret poorly drafted requirements such as that research may only be authorised if the parent or minor's reasons for consenting to the research are not contrary to public policy.
3. Certain ethical guidelines are restrictive in their approach, e.g. the Medical Research Council's General Principles[6] permit parents to enroll their children in 'non-therapeutic' research only if it is 'observation' research, and research with risks not exceeding everyday life. This approach may prevent the enrolment of healthy children in intervention research such as clinical trials of prevention products.

Recommendations

A number of recommendations were made at the forum to promote a more coherent framework that facilitates critical research with child participants, including adolescents, while promoting their rights and welfare. These included the following.

Capacity should be built for stakeholders to better understand the strengths, weaknesses and implications of the framework, and mechanisms should be developed to allow them to impact on the framework

It was recognised that in many instances stakeholders felt unable to participate in the ethical-legal framework or impact on its development because of a lack of capacity. Accordingly it was recommended that: (*i*) the capacity of community representatives, RECs and investigators should be developed to enable them to understand the relevant laws and guidelines, and their interpretation in relation to HIV vaccine research; (*ii*) an accurate understanding of the perspectives and concerns of participating communities should be established through sensitive research and consultation; and (*iii*) mechanisms should be developed whereby stakeholders, such as RECs, can liaise on the interpretation of laws or guidelines in order to aspire towards consistent protocol review.

Law reform and the revision of ethical guidelines is required

The following was recommended: (*i*) input should be made to the regulations that will accompany the National Health Act in order to resolve certain inconsistencies and ambiguities in the Act;[3] (*ii*) proposals to include the rights of child research participants in the Children's Bill[4] should be supported; and (*iii*) revisions should be made to ethical guidelines[5,6] that ensure their harmonisation and ability to protect child participants while accommodating sound research.

Appropriate tools should be developed

It was recommended that tools and tests should be developed to facilitate the appropriate implementation of a number of the new requirements set out in the National Health Act including: (*i*) children's 'understanding' of research participation; (*ii*) determining 'public policy'; and (*iii*) determining the 'best interests of the child'.

In conclusion, a transitory and inconsistent framework complexifies research involving adolescent or child participants. Considerable training, law reform, guideline amendment and tool development are required to better protect these participants and to facilitate critical research to promote their health.

The authors would like to thank members of the South African AIDS Vaccine Initiative's Adolescent Working Group for their comments on the paper, and in particular Dr C Metcalf. The paper could not have been written without the input of the participants at the forum held by the HIV AIDS Vaccines Ethics Group.

HAVEG is funded by the South African AIDS Vaccine Initiative.

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Accepted 17 May 2005.