

Reye's syndrome and aspirin

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Introduction

REYE'S syndrome is a severe disorder almost entirely limited to children and characterized by encephalopathy and fatty infiltration of the viscera, especially the liver. Typically the child seems to be recovering from a viral or other febrile illness when severe vomiting and altered consciousness occur. Unexpected protracted vomiting following a prodromal influenza-like illness, chicken pox or other febrile condition is characteristic, but infants and children under three years of age may have minimal vomiting and no clear prodrome. The condition should be suspected when, in these circumstances, there are signs of disturbed brain function including lethargy, staring, stupor, agitated delirium, screaming, rapid respiration, extensor spasms, decerebrate rigidity, involuntary movements and coma. Hypoglycaemia and hepatomegaly are sometimes present in Reye's syndrome as are grossly elevated serum transaminase levels, usually associated with raised blood ammonia levels, despite the absence of jaundice. The outcome is frequently death or survival with severe brain damage.

The British Reye's Syndrome Surveillance Scheme was started in August 1981 and in the first four years of surveillance 229 cases of Reye's syndrome were reported. One hundred and fifteen of these children died. In the United Kingdom the annual incidence has varied from 0.3 to 0.7 per 100 000 children under 16 years of age during the surveillance period. In view of the poor prognosis, and the fact that early treatment can be effective, a high index of suspicion is essential, even though the illness is rare. To achieve early diagnosis the condition should be suspected by the general practitioner and emergency liver function tests, prothrombin time estimations and measurements of blood ammonia levels should be undertaken immediately following urgent admission to hospital.

The initial treatment comprises infusions of 10% glucose solution to provide 70% of maintenance fluid requirements, estimation and correction of altered blood sugar values, maintenance of a proper airway and normalization of abnormal blood gas levels. Urgent measures to control raised intracranial pressure should be instituted while arrangements are made for transfer to a paediatric intensive care unit with facilities for measuring intracranial pressure accurately. Highly specialized techniques for controlling the grossly abnormal blood and tissue biochemistry produced by the syndrome have been described.^{1,2}

Background

Vague descriptions of what may have been Reye's syndrome have appeared in the medical literature since 1929. The condition was

All suspected cases of Reye's syndrome should be reported to the British Reye's Syndrome Register (Public Health Laboratory Service Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, telephone: 01-200 6868). Posters can be obtained from the National Reye's Syndrome Foundation of the United Kingdom (22 Wellands, Wickham Bishops, Witham, Essex). Patients who would like additional information on Reye's syndrome and aspirin use by children will find the *Healthline* tape no. 20 helpful (College of Health, telephone: 01-980 4848 between 14.00 and 22.00 hours).

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first described as a distinct clinical entity by the Australian pathologist R. Douglas Reye in 1963.³ The condition appears to have a multifactorial aetiology and no single cause has yet been identified. Several factors may be necessary for the condition to appear and these are likely to include some inborn hypersensitivity or genetic/metabolic factor associated with an abnormal response to a viral infection in the presence of a chemical trigger. Insecticides and, more recently, aspirin have been implicated in studies in the USA. The evidence so far available suggests that aspirin may be a contributory factor in causing some cases of Reye's syndrome and the weight of this evidence, together with the serious nature of the condition and the availability of alternative appropriate remedies, such as paracetamol, has led the Committee on Safety of Medicines to advise that aspirin should not be given to children under 12 years of age unless it is specifically indicated for childhood rheumatic conditions.

Aspirin and the development of Reye's syndrome

There are essentially three lines of thinking which suggest an association between the use of aspirin and the development of Reye's syndrome.

Case control studies

During an outbreak of influenza A in Arizona in December 1978, a study was made of seven patients with Reye's syndrome and 16 ill classmates as controls.⁴ It was found that all seven patients had taken salicylates whereas only eight of the 16 controls had done so ($P < 0.05$).

In Michigan⁵ during the winter of 1979-80, 56 cases of Reye's syndrome in school-age children were reported to the Centre of Disease Control. The parents of 25 of these children were interviewed in the spring of 1980, as were control subjects matched to the cases for age, race, school grade and nature of any antecedent viral illness. It was found that more children with Reye's syndrome had received aspirin during their viral illness (24 out of 25 cases) than controls (34 out of 46).

A second study was undertaken in Michigan⁵ during the winter of 1980-81. Again it was found that more children who had Reye's syndrome had received aspirin-containing products during their viral illness (12 out of 12 cases) than control subjects (13 out of 29).

In Ohio⁶ 97 cases of Reye's syndrome occurring between December 1978 and March 1980 were compared with 156 control subjects matched for age, race, sex, geographic location, time, and type of illness. Only the use of aspirin was found to be significantly different between the cases and controls: 94 (97%) of the 97 cases compared with 110 (71%) of the 156 controls had taken aspirin.

The Centre of Disease Control in the USA obtained the assistance of outside consultants to review these four studies which all had methodological problems such as selection bias, inappropriate control selection, recall bias and protopathic bias. On the basis of this review the US Food and Drug Administration concluded that the studies did not establish a conclusive link between the use of aspirin and the development of Reye's syndrome. In 1982, at the instigation of the Food and Drug Administration, the US Public Health Service developed a plan for a much larger study designed to overcome these methodological difficulties. The Food and Drug Administration also instituted an educational programme aimed at the general public and the

health community warning against the use of aspirin in children who had suffered from influenza and chicken pox.

In 1984 the preliminary results from the pilot phase of the Public Health Service study became available and the full report⁷ was published in October 1985. Thirty patients with Reye's syndrome, whose diagnosis had been confirmed by an expert panel, and 145 controls were matched for age, race, and antecedent illness and selected from the same hospital, emergency room or school or identified by random digit dialling. Significantly more cases, 28 (93%) out of 30, than members of each of the four control groups or all controls combined, 66 (46%) out of 145, had received salicylates during the antecedent illness. (The odds ratio of all 30 cases versus all controls was 16.1, the lower 95% confidence limit was 4.6.)

The British Reye's Syndrome Surveillance Scheme was started in 1981 as a joint activity run by the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre. In 1985 the Committee on Safety of Medicines was able to consider the preliminary results of the US Public Health Service pilot study and the data then available from the British scheme. It was apparent that Reye's syndrome in the UK differs from the clinical picture in the USA. The median age of 14 months in the UK was much less than in the USA; there were no obvious winter peaks in the number of reports of Reye's syndrome in the UK and no significant association with influenza. In the UK study there was a lower incidence of a clearly defined prodromal illness but the mortality was substantially higher than in the American studies.

None of the studies mentioned so far proved a direct link between the use of aspirin and the occurrence of Reye's syndrome. The situation was therefore kept under the closest scrutiny. In 1986 additional data, now being prepared for publication, became available from the British study. These data, reviewed in confidence by the Committee on Safety of Medicines, added to the weight of evidence already available and formed an appropriate basis for action. The factor that was persuasive was that all six available studies showed a finding in the same direction and suggested, albeit with varying degrees of significance, an association between the use of aspirin and the development of Reye's syndrome in some children.

British Reye's Syndrome Surveillance Scheme study data

During this study Dr Susan Hall, the principal investigator, and her colleagues interviewed the parents of 106 of the 229 reported cases in order to obtain a detailed review of possible aetiological factors. Careful analysis has shown that by ranking the Reye's syndrome subjects in groups reflecting the degree of confidence in the diagnosis, a clear trend is established showing that a greater proportion of the children with the most clear-cut diagnosis had taken aspirin; conversely, a smaller proportion had taken aspirin in the groups in which the diagnosis was less certain. Publication of the detailed data underlying this association is, of course, eagerly awaited because the analysis, ingenious in its own right, is unaffected by most of the biases introduced into earlier studies and is independent of any statistical difficulties in comparing cases and controls. This is especially important in the British Reye's Syndrome Surveillance Scheme study in which a comparison group of patients was studied but these subjects were not formal case controls.

Recent information

Remington and colleagues⁸ have studied the decrease in the numbers of cases of Reye's syndrome and the use of aspirin in Michigan over the period 1979–84 and have produced data which strongly suggest that a reduced use of aspirin may be associated with a decrease in the incidence of Reye's syndrome. In February 1986 the *Morbidity and Mortality Weekly Report*^{9,10} revealed

a marked fall in the number of case reports of Reye's syndrome in the USA in 1985: in 1984 204 cases of Reye's syndrome had been reported but this had dropped to 91 cases in 1985. Although delayed reports may increase this latter number slightly, this total is less than half the lowest annual total reported since 1973 when the surveillance of Reye's syndrome began in the USA. It is certainly plausible that this marked fall in the incidence of Reye's syndrome may reflect the reduced use of aspirin in the relevant population. This reduced use of aspirin in the USA seems likely to have followed warnings issued by the Food and Drug Administration and carried into legislation in 1985. It is therefore to be hoped that diminishing aspirin use in young children with febrile illnesses in the UK may be associated with a reduced incidence of Reye's syndrome in this country.

The decision of the Committee on Safety of Medicines

On 26 March 1986 the Committee on Safety of Medicines concluded, on the basis of the available evidence and the new data from the British Reye's Syndrome Surveillance Scheme study, that the use of aspirin in feverish illness may be a contributory factor to the causation of Reye's syndrome in some children and that there was a need for action to reduce the use of aspirin in children. The Committee advised that warning labels should be applied to all oral preparations of aspirin showing that they should not be used for feverish illnesses in children without medical advice and that paediatric preparations of aspirin should be removed from the general sales list. The Committee also advised that an urgent educational campaign should be undertaken to alert doctors and parents to the possible risks associated with the use of aspirin in febrile illnesses in young people.

When this advice was put to the Proprietary Association of Great Britain and those segments of the pharmaceutical industry which market aspirin, the Association indicated a willingness to cease distribution of paediatric aspirin preparations and support the labelling and educational programmes advocated. In accepting these proposals the Committee on Safety of Medicines commented that it was of fundamental importance that the British Reye's Syndrome Surveillance Scheme should be continued and that the effectiveness of the measures to be taken should be carefully monitored.

On 9/10 June 1986 Professor Sir Abraham Goldberg, Chairman of the Committee on Safety of Medicines, wrote to all doctors, dentists and pharmacists recommending that aspirin should no longer be given to children aged under 12 years unless specifically indicated, for example, for juvenile rheumatoid arthritis. The age of 12 years had been chosen as the British Reye's Syndrome Surveillance Scheme study had shown that 93% of reported British cases of Reye's syndrome were in children under this age. The letter was despatched slightly earlier than had been planned owing to media reports that some such announcement was imminent. These reports negated the Committee's express intent of notifying the medical and pharmaceutical profession 48 hours or so before general advice was issued. The Chairman's letter also announced the industry decision that paediatric aspirin products would be withdrawn from sale.

On 10 June the Government's Chief Medical Officer held a press conference and this was followed by a press announcement issued by the Aspirin Foundation in consultation with the Department of Health and Social Security.

On 14 June, the article 'Reye's syndrome and aspirin'¹¹ summarized the available data and emphasized the fact that, whereas all four of the separate American studies had shown a positive association between aspirin consumption and the development of Reye's syndrome, no less than three of these studies had shown a negative association with paracetamol. The important point was also made that most of the British patients with Reye's syndrome had been aged under six years and 93% under 12 years.

Questions and comments

Complex actions by the Committee on Safety of Medicines and Licensing Authority sometimes generate written comments and questions and there have been a number of letters from the medical profession on the action taken on aspirin and Reye's syndrome.

Too soon or too late?

Unlike some parliamentary and press comment, few doctors — judging from the letters received — believed that action should have been taken earlier. A small number commented that the action had been precipitant, as the data fell short of proof. Some asked how many of the cases of Reye's syndrome in the British study had, in fact, taken aspirin. The answer, for which acknowledgement is made to Dr Susan Hall, is that the preliminary data show that 63 (59%) of the 106 Reye's syndrome cases interviewed in the risk analysis section of the study gave a history of aspirin ingestion in the three weeks before hospital admission.

It seems clear that Reye's syndrome can occur in the absence of aspirin ingestion. It is therefore unlikely that the present action can do more than diminish the real incidence (and possibly the severity) of the syndrome. In the face of 115 deaths in British children in the last four years the present data, in the opinion of the Committee, provide an adequate basis for action taken in the hope of reducing this toll. But a spectrum of opinion, when the data are complex and not yet all in the scientific domain and, in any case, fall short of proof, is the prerogative of the profession. A range of views is to be expected when the risk of a rare, but often fatal, syndrome must be balanced against the benefit of a drug which has been used on a vast scale, and widely regarded as safe and effective, since its introduction in 1899. What is clear is that the new data now available have been found persuasive following exhaustive review by the Committee on Safety of Medicines, which has had access to information awaiting publication, and which has also been able to assess the differences in the manifestations of Reye's syndrome in the USA and the UK. The Committee has timed the introduction of measures to protect the public health in this country in the light of these facts, and the overall benefit to risk assessment.

What about other salicylates?

A very small number of children with Reye's syndrome in the British study had taken salicylates other than aspirin, but they had all also taken aspirin itself. The view of the Committee on Safety of Medicines was that there was no evidence presently available of an association between Reye's syndrome and salicylates other than aspirin. Aspirin has been shown to be superior to other forms of salicylate in experimental studies of chronic arthritis and the acetyl radical appears to be a critical factor in the anti-inflammatory action of the drug.¹² Thus, there are real differences between aspirin and other salicylates and it is essential that there should be relevant data if rational decisions are to be taken on the use of non-aspirin salicylates in the age groups in which Reye's syndrome is known to occur. The present action is therefore limited to products which are taken orally and which contain aspirin or form aspirin on absorption or metabolic change in the body. It therefore includes, for example, benorylate and aloxiprin. It does not include topical applications such as the teething gels containing choline salicylate. One case which may link Reye's syndrome with such a teething gel has been reported in the lay press and is currently under investigation. Teething gels of this type have also been reported¹³ to cause salicylate intoxication when used in doses in excess of the recommendations of the manufacturers.

Labelling of aspirin products

According to existing labelling regulations aspirin products currently on general sale have to bear the following warnings: 'Contains aspirin'; 'If symptoms persist consult your doctor'; and 'Keep out of reach of children'. As early as possible, and certainly by early 1987, adult oral aspirin preparations will also carry warnings indicating that they should not be given to children under 12 years of age except on medical advice.

Can aspirin be given in juvenile chronic arthritis?

The British study¹⁴ included two cases of Reye's syndrome in children given aspirin for chronic inflammatory disorders. Thus it would seem that there is a risk, but it may be outweighed by the risk of not using aspirin in these difficult circumstances. The decision is one the individual general practitioner must make acting upon his own assessment of the benefit to risk considerations in the individual patient. It is clearly important that careful notes should be kept of this assessment.

75 mg aspirin tablets for adults

This subject has produced more letters from practitioners than any other. In the UK no aspirin product has anti-platelet or anti-thrombotic activity as a licensed indication. Nevertheless, doctors are exempt from certain provisions of the Medicines Act 1968 and, by virtue of Section 9 of that Act, medical practitioners can prescribe in accordance with their own professional judgement for their individual patients. Some of the traditional suppliers of paediatric aspirin tablets have recently varied their product licences in order to make 75 mg aspirin tablets available through pharmacies for use in complying with prescriptions of this type. These dispensing packs of 75 mg aspirin tablets will carry warnings showing that the product should not be given to children under 12 years of age except on medical advice.

Is aspirin safe in pregnancy and the perinatal period or when breast-feeding?

Reye's syndrome has not been reported in the fetus. To date, no studies of the histopathology of the fetal brain and liver of still-born children whose mothers have ingested aspirin during pregnancy have been published. Theoretically it would seem unlikely that the fetus would be at risk of Reye's syndrome, particularly if a sensitizing viral infection is an essential or common precipitating factor. Thus, present knowledge does not point to, but does not necessarily exclude, a fetal risk from Reye's syndrome.

The general risks of aspirin ingestion in pregnancy are largely limited to the third trimester and include impaired platelet function and the risk of haemorrhage; kernicterus in jaundiced neonates; closure of the fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of the newborn child with the regular use of high doses of aspirin; and delayed onset and increased duration of labour with increased blood loss when aspirin is used in the last week of pregnancy. The general risks of aspirin during breast-feeding are the occurrence of rashes and hypoprothrombinaemia (with inadequate neonatal vitamin K stores) in the infant. It is therefore advised that regular high doses of aspirin should be avoided in advanced pregnancy and salicylates should not, if possible, be used in the week before term. As, in Britain, Reye's syndrome has its greatest incidence in the very young it would seem prudent to advise that aspirin should not be taken by mothers who are breast-feeding.

The dangers of paracetamol

Paracetamol forms an acceptable alternative to aspirin in children. It is excreted in the breast milk in significant amounts but these are not known to be harmful to the infant when only conventional doses have been ingested by the mother.

Paracetamol is similar in antipyretic and analgesic activity to aspirin but has no demonstrable anti-inflammatory activity.

Paediatric paracetamol elixir has for some time been considered preferable to aspirin for infants and the present action, in effect, extends this statement throughout the whole period of childhood. The disadvantage of substituting paracetamol for aspirin is that overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for four to six days. Doctors should therefore consider coupling their advice regarding the use of aspirin in children under 12 year of age with warnings that the conventional doses of paracetamol should in no case be exceeded. The Committee on Safety of Medicines and its Secretariat have made careful arrangements to monitor the number of reported cases of paracetamol overdose.

Conclusion

Assessment of the effects of the present action to restrict the use of aspirin in children aged under 12 years is clearly of crucial importance. Doctors are asked to be particularly diligent in reporting suspect adverse reactions to paracetamol by means of the yellow card scheme and, while it is perhaps appropriate that doctors should be on their guard against being influenced in diagnosing Reye's syndrome by their knowledge of whether or not aspirin has been given, it is of special importance that suspect cases of Reye's syndrome should be reported to the British Reye's Syndrome Register (telephone 01-200 6868).

It is possible that the number of cases of Reye's syndrome suspected may now increase (rather than diminish) owing to the increased awareness of the profession. Thus care must be exercised in interpreting future statistics on the apparent incidence of the condition.

It is hoped that the advice of the Committee on Safety of Medicines on restricting the use of aspirin in children under 12 years of age will reduce the levels of mortality and morbidity caused by Reye's syndrome in the UK. However, the final outcome depends on doctors and pharmacists bringing the message home to parents and to their children.

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