Reye Syndrome and Salicylates

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This year in the United States there has been considerable controversy about circumstantial evidence linking salicylates to the pathogenesis of Reye syndrome and, in particular, whether that evidence is sufficiently strong to justify action. After careful review both the Federal government and the American Academy of Pediatrics have warned physicians and parents of the possible risk of Reye syndrome in children who receive aspirin for varicella or influenza-like illnesses.

For the past several years between 200 and 500 cases of Reye syndrome have been reported under a voluntary surveillance system. Undoubtedly many cases are not reported; the Centers for Disease Control estimates that the true annual figure is probably 600 to 1200 cases. Extrapolation of data from Ohio and Michigan where surveillance has been more intense suggests the number may be even higher—1600 to 3200 cases annually. Case-fatality rates range from 22 to 42%. The majority of cases of Reye syndrome have been associated with influenza, usually influenza B; in approximately 20% of cases the inciting illness is chicken pox; the remainder are associated with a variety of other viral illnesses. Hypotheses to explain why only certain children with these viral illnesses develop Reye syndrome have ranged from genetic predisposition to various environmental factors, such as insecticides, and to medication administered for the antecedent viral illness. But these were only hypotheses until the second half of 1980, when summaries of five case control studies of Reye syndrome conducted in Arizona, Ohio and Michigan were published. Full reports of these studies are now published.

In these studies parents of children with Reye syndrome were asked a wide variety of questions concerning the child’s immediate and past history, focusing particularly on exposures to potentially toxic substances and on medications given during the inciting viral illness. For each case one or more control children, absent from the child’s classroom with what appeared to be the same viral illness, were selected and identical interviews conducted. Each of the five studies demonstrated a statistically significant association of Reye syndrome with aspirin administration during the prodromal illness compared to controls. In total all but four of 141 children with Reye syndrome were reported to have received aspirin, compared to 151 of 247 control children. Additionally, in the four largest of the five studies a reverse association with acetaminophen was observed, in that controls were reported to have received this drug more often than patients. On the basis of these preliminary reports the Centers for Disease Control and the American Academy of Pediatrics early in the winter of 1981–2 issued rather tentative warnings to physicians about salicylate usage in children with influenza or chicken pox.

In an effort to clarify the matter and to develop more definitive recommendations, the Centers for Disease Control assembled a panel of outside consultants in October 1981 to review the five studies in greater detail. Although the panel noted the difficulties inherent in case control studies in general and identified specific problems in these five studies, they nonetheless concluded that the evidence of a causative relationship of salicylates to Reye syndrome was sufficiently strong to warrant a firm warning, with the caveat that the issue needed further study. A summary of the panel’s recommendation was published in February 1982.

These studies were also reviewed by the Committee on Infectious Diseases of the American Academy of Pediatrics, which similarly concluded that the association was unlikely to be attributable to methodological defects. Therefore, in March 1982, the Academy issued a strong warning to paediatricians, followed by an explanation of the Committee’s rationale in June.

Subsequently, the five studies were reviewed by epidemiologists and statisticians of the Food and Drug Administration, who had the additional advantage of availing themselves of the raw data. The FDA analysis reaffirmed and strengthened the conclusion of the two prior reviewing groups. Accordingly, on 4 June 1982, the Secretary of the US Department of Health and Human Services, Mr Richard S Schweiker, issued a public warning about the use of salicylates in children with chicken pox or influenza-like illnesses, ordered an educational programme for health care providers, parents and pharmacists, and mandated an appropriate warning label on aspirin products.

Debate in the US concerning these conclusions and recommendations has been considerable, though not achieving the intensity of that concerning pertussis.
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vaccine in Britain. The debate centres around four particular problems inherent in these conclusions and recommendations. First, the results of these studies are not incontrovertible because of design problems and because the association between salicylates and Reye syndrome is not as strong, for example, as that between tampon usage and the toxic shock syndrome. Second, parents and physicians are placed in a difficult position; a recommendation to avoid salicylates in children suspected of influenza epidemiologically or because of the nature of the illness is imprecise at best. A great many childhood illnesses are 'influenza-like', at least at their inception. The recommendation thus implies that no child with a fever should receive salicylate. Third, how does one assess the benefit/risk ratio of salicylate usage in children with such problems as rheumatoid arthritis, which is often controlled by salicylates, in view of anecdotal evidence that they are at higher risk for Reye syndrome? Fourth, these recommendations cause concern among physicians in the US in terms of malpractice litigation; how can a physician warn all of his or her patients?

Representatives of the US aspirin industries have voiced the most vigorous objections, on the grounds of methodological flaws in the five case-control studies. In particular they assert that the more frequent use of salicylates for the antecedent illnesses of the cases was prompted by greater severity of these illnesses. However, in one review of these studies it was pointed out that, because of slight differences among the methods used in the five studies, problems apparent in one study were often answered by another.10

Balancing the benefits of salicylates in these viral illnesses with the probable risk even in the absence of certainty, the only prudent course of action seemed to be to issue a warning. But the dust has not yet settled.

REFERENCES


OBITUARY
DR. ABDUL HUSAIN TABA

It is with deep sorrow and a sense of bereavement that we received the sad news of the untimely death of Dr Abdul Husain Taba on 8 July, 1982 in Geneva.

I have known Dr Taba for a long time not only as a personal amiable friend and brilliant colleague but also as a dedicated scientist and an administrator of the highest calibre. He was made an Honorary Life Member of the International Epidemiological Association, the highest honour, conferred upon only some twelve members since the Association's inception, in recognition of his energetic promotion of the work of the Association at both regional and international levels.

He was always a good companion and his death is a great loss to us all.

Dr S Al-Tikriti,
Director General of Public Health and Social Medicine,
Iraq, and IEA Council member for the Eastern Mediterranean Region.