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Is Aspirin a Cause of Reye's Syndrome?

In a paper published in *Drug Safety* in 2002, Orlowski et al. attempt to convince readers that aspirin (acetylsalicylic acid) is not a causal factor in the aetiology of Reye's syndrome.[1] They argue that although aspirin "may be associated" it is "unlikely, illogical and unfounded" to state that this is a causal association. In their conclusions the authors reiterated the question posed by the title above and gave the answer "definitely not". We consider below the extent to which the arguments put forward by Orlowski et al. support their views.

Orlowski et al. point out various limitations of the epidemiological evidence linking aspirin to Reye's syndrome and the lack of a clearly defined mechanism to explain such an effect. These arguments have some merit but do not in themselves exclude a causal effect. Neither having evidence that is less than ideal nor being unable to explain a postulated effect is sufficient to refute an association in the definitive manner suggested by these authors. In addition, they advance nine more specific arguments to support their case. In the order put forward by the authors, these may be summarised as follows:

1. Reye's syndrome did not exist before 1950 – it suddenly appeared in the 1950s but aspirin had been used since 1899; paracetamol (acetaminophen) was discovered in 1955.

2. Reye himself concluded that aspirin was not a cause of the syndrome.

3. "Association can never be used to prove causation" (and, later, "you can never prove anything with statistics").

4. Aspirin ingestion occurred in patients with viral illnesses who did not develop Reye's syndrome.

5. Uncertainty about the timing of the onset of the syndrome – whether the data are analysed with protracted vomiting or the onset of altered mental status as the starting point is material to whether or not an association with phenothiazines is found.

6. International differences in patterns of the disease and association with aspirin.

7. Koch's postulates are not fulfilled.

8. Reye's syndrome was disappearing before label warnings were introduced in 1986.

9. Some cases of Reye's may have had undiagnosed inborn errors of metabolism.

Most of these points listed above have some truth in them but the main issue is whether they are convincing arguments against a causal association between aspirin and Reye's syndrome. In that respect, our comments on each are as follows:

1. The hypothesis here is that aspirin may be one causal factor in a multifactorial aetiology (perhaps a trigger in already susceptible individuals). If it is true that Reye's syndrome did not exist until 1950 (and it is hard to be sure of this) then that could reflect the infectious component of the disease (perhaps a viral mutation as the authors suggest). The prior availability of aspirin would then be irrelevant because the people using it would not have been susceptible.

2. Reye's own conclusion is cited by Orlowski et al. to the article he published in 1963 describing the syndrome – at least 15 years before most of the epidemiological evidence became available. Reye was not an epidemiologist and there is no reason why we should place particular weight on the views on aetiology of someone who describes a clinical syndrome.

3. Almost invariably, assessing an association between a drug and a possible adverse effect is a matter of making a judgement based on all the available evidence rather than conclusive proof. The point that statistical and epidemiological data cannot provide absolute proof of a causal link between aspirin and Reye's syndrome does not mean that such evidence can be ignored altogether.

4. It is not surprising that, in a case-control study, some controls are exposed to the putative causal agent (otherwise the relative risk will be infinite). What is much more impressive is the very high level of exposure to aspirin in the studies cited (figures of 97%, 93% and 96% are quoted) and lack of association with paracetamol (which is not mentioned by these authors).

5. In order to be sure of a correct temporal association it is sensible to define the onset of the syndrome earlier (vomiting) rather than later (altered mental state). The fact that if the latter definition is used an association can be found with a treatment for vomiting is entirely unsurprising and adds nothing to this debate.

6. The incidence of Reye's syndrome has indeed been enormously variable in time and place. However, this is unsurprising given that there is undoubtedly an infectious component to the aetiology.

7. Koch's postulates may still be useful in assessing the evidence for causation of infectious diseases but for other causes, including drugs, Bradford-Hill's criteria [2] are used to evaluate the strength of evidence that an association is causal.

8. It is undoubtedly true that the decline in incidence of Reye's syndrome started before 1986. Figure 1 in the paper by Orlowski et al. plots the incidence of Reye's syndrome in the US from 1973–1999 and shows that a steady decline was evident after 1980, 6 years before labelling changes. However, 1980 saw the first reports of an association between aspirin and Reye's syndrome, and the Surgeon General issued an 'advisory' in 1982. Public awareness of the link with aspirin and/or other unidentified factors may have started the decline in Reye's syndrome before definitive regulatory action was taken in 1986.[3] To use an historical analogy, factors such as improved nutrition and sanitation were important in reducing the incidence of tuberculosis well before BCG vaccine was introduced.

9. Uncertainty about the diagnosis of Reye's syndrome is one of the difficulties hampering the investigation of this association. However, in principle, including cases that are incorrectly diagnosed in studies will tend to weaken a real association rather than create a spurious one. Moreover, inborn errors of metabolism do not account for all cases of Reye's syndrome and the condition is still diagnosed in its own right today, albeit very rarely.

The paper by Orlowski et al. attempted to argue that there is no causal association between aspirin and Reye's syndrome.[1] In our view, the arguments they put forward for this were individually weak and collectively insufficient to support their case. There is no doubt that the evidence for an association between aspirin and Reye's syndrome has limitations and that our understanding of the aetiology of this syndrome is incomplete. Not all of Bradford-Hill's criteria are met but the strength, consistency and specificity (i.e. lack of association with other treatments used in children with viral illnesses) of this association, as demonstrated in epidemiological studies, suggest to us that a contributory causal effect is a much more likely explanation. Orlowski et al. comment on the limitations and possible biases associated with epidemiological studies conducted in the early 1980s. However, they fail to acknowledge the considerable efforts that were made in the later study by Forsyth et al., published in 1989,[4] to overcome many of these pitfalls. This study also found a very strong association between aspirin and Reye's syndrome.

Given the widespread availability of alternative treatments for which there is no suspicion of a link with Reye's syndrome, the evidence available in 1986 was a reasonable basis on which to take action aimed at preventing a lethal disease occurring in children. Published data and patterns of disease epidemiology since avoidance of paediatric aspirin use was recommended[3-5] strengthen rather than weaken the case for a causal association.

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Conflicts of Interest

Rafe Suvarna is currently an employee of the UK Medicines and Healthcare products Regulatory Agency (formerly Medicines Control Agency); Patrick Waller was employed there from 1990–2002.

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