Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Evaluation Committee

Review of Aspirin / Reye's syndrome warning statement

April 2004

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Prepared for the TGA by Dr Susan James

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REVIEW OF ASPIRIN/REYE'S SYNDROME WARNING STATEMENT

Acknowledgments

The review wishes to acknowledge the assistance of:
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Abbreviations

MEC – Medicines Evaluation Committee
TGA – Therapeutic Goods Administration
NDPSC – National Drugs and Poisons Scheduling Committee
CSM – Committee on Safety of Medicines
ADRAC – Adverse Drug Reactions Advisory Committee
NTGC – National Therapeutic Goods Committee
SUSDP – Standard for the Uniform Scheduling of Drugs and Poisons
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
BRSSS – British Reye's Syndrome Surveillance System
CDC – Centres for Disease Control
PHS – Public Health Service
BPSU – British Paediatric Surveillance Unit

Introduction

Background

As part of the *Review of non-prescription analgesics* (1998) and the subsequent *Review of non-prescription analgesics – an update* (2003) (hereafter referred to as *"the Update"*), recommendations were made regarding changes to the cautionary and advisory statements required on the labels of non-prescription analgesics containing aspirin or NSAIDs. After recent changes to the recommended aspirin warning statements regarding Reye's Syndrome in the UK, the Update recommended consideration of the UK warning statement for adoption in Australia.

At its meeting on April 3 2003, the MEC agreed to re-examine the evidence linking aspirin use in children or teenagers with chicken pox, influenza or fever, with Reye's Syndrome, with a view to making further recommendations to the NDPSC about the advisability of adopting the UK warning statement. The purpose of this review is to provide advice on the current evidence linking aspirin use in children or teenagers to Reye's Syndrome and the suitability/necessity of adopting the UK warning statement.

Terms of Reference

1. Obtain and review data on any association between aspirin use in children and teenagers and the development of Reye's Syndrome. Relevant data to be identified by literature search conducted by TGA Library staff.
2. In view of the evidence reviewed, consider the appropriateness of the current SUSDP Appendix F warning statement for aspirin (Consult a doctor before giving this medication to children or teenagers with chicken pox, influenza or fever). Consider also the appropriateness of the new UK warning statement (Do not give to children under 16 years of age unless on the advice of a doctor), and any other relevant warning statements adopted by overseas regulatory authorities.
3. Consult with professional persons or bodies as necessary following agreement with the OTC Medicines Section.
4. Make recommendations to the Therapeutic Goods Administration and the Medicines Evaluation Committee about the suitability of retaining the current SUSDP Appendix F warning statement for aspirin, adopting the new UK warning statement, or adopting a revised warning statement.
5. Return all documentation to the TGA on completion of the project.

History of Appendix F warning statement

The current warning statement required on scheduled and unscheduled OTC aspirin-containing products ("*Consult a doctor before giving this medicine to children or teenagers with chicken pox, influenza or fever"*) was introduced into Appendix F of the

SUSDP at the 50th meeting of the DPSC in August 1988, after discussion of the issue and recommendations made by ADRAC and NTGC during the period 1986-1988. The warning statement had already been voluntarily placed on a number of aspirin-containing products (since 1986) prior to this regulatory action in 1988. The introduction of the warning statement was not based on specific Australian Reye's Syndrome statistics, but on the action taken in the UK in 1986 to require the warning statement "Aspirin should not be used in children aged less than 12 years except on medical advice" on aspirin-containing products.

Recent Overseas regulatory action

Regulatory action concerning warning statements on aspirin products has been taken recently in both the UK and the USA.

UK action

In the UK, at several meetings during 2002, the CSM discussed the need to amend its existing warning statement (*"Aspirin should not be used in children aged less than 12 years except on medical advice"*), which was introduced in 1986. At its meeting on 13 March 2002, the CSM recommended a revised warning statement *"Do not give aspirin to children under 12 years unless medically indicated, and avoid in children aged up to and including 15 years if feverish"*. A subsequent meeting on 16 October 2002 noted concerns that the proposed warning statement was too complex, and recommended that the statement be revised to *"Do not give to children under 16 years of age, unless on the advice of a doctor"*. This warning statement is required on all aspirin-containing products in the UK from October 1, 2003.

The basis of this recommendation was data from the British Paediatric Surveillance Unit (BPSU) showing that from 1986 until 1999, there were a total of 17 cases of Reye's Syndrome associated with aspirin use in the UK: 7 in children under 12 years of age, and 10 in those aged 12 – 15 years. An additional 5 cases of Reye's syndrome over the age of 12 did not have any evidence of aspirin exposure (Committee on Safety of Medicines 2002).

USA action

In 1986, the FDA issued a final rule requiring a warning statement (*"Children and teenagers who have or are recovering from chicken pox, flu symptoms or flu should NOT use this product"*) on all oral and rectal OTC drug products containing aspirin. In 1993, the FDA issued a notice of proposed rule making to require an amended warning statement (*"Children and teenagers who have or are recovering from chicken pox, flu symptoms or flu should NOT use this product. If nausea, vomiting, or fever occur, consult a doctor because these symptoms could be an early sign of Reye's Syndrome, a rare but serious illness."*) on OTC overindulgence drug products containing bismuth subsalicylate. Subsequent amendments to the proposed rule resulted in a final rule issued on 17 April 2003, requiring the above amended warning on all oral and rectal OTC drug products containing aspirin, and on OTC drug products containing non-aspirin

salicylates, from April 19 2004 for products with total sales over US$25,000 and from April 19 2005 for products with total sales less than US$25,000. It is notable that a recommendation for the inclusion of the early symptoms of Reye's Syndrome in the 1986 warning were rejected by the FDA at the time.

The basis for the recent FDA action is a series of case reports indicating 15 potential cases of Reye's Syndrome in the period 1989 to 1997 in patients who took bismuth subsalicylate-containing products (Food and Drug Administration 2003). All the patients whose ages were recorded were under the age of 15. Three of these patients also took aspirin. The FDA admits that it does not have definitive evidence of an association between non-aspirin salicylates and Reye's Syndrome, but argues that the number of case reports provides sufficient suggestion of an association to take action. The FDA also refers to in vitro studies suggesting that the salicylate moiety may be involved in the mitochondrial injury observed in some Reye's Syndrome cases. However, the FDA admits that the actual pathogenesis of Reye's Syndrome is not known.

What is Reye's Syndrome?

Reye's Syndrome was first described by Reye in 1963, who reported on a series of 21 children admitted to the Royal Alexandra Hospital for Children in New South Wales over the period 1951-1962, with acute encephalopathy and fatty changes in the liver (Reye et al 1963). In the same year, Johnson reported on 16 fatal cases of encephalitis-like disease occurring during an influenza B outbreak in North Carolina (Johnson et al 1963). Reye's Syndrome is currently defined by the BPSU as *"an unexplained, non-inflammatory encephalopathy in those less than 16 years of age, associated with serum aspartate or alanine aminotransferases, or plasma ammonia more than three times the normal limit, or hepatic fatty infiltration that is microvesicular in appearance and panlobular in distribution"*. The Centres for Disease Control (CDC) in the United States definition is similar *"a child under 18 years with (1) an acute non-inflammatory encephalopathy (without CSF pleocytosis), (2) characteristic liver histology or raised serum transaminases or ammonia values (≥ 3x normal) and (3) no other explanation for the illness"*. However, it is recognised that these are rather non-specific definitions, since other conditions (such as drug reactions, infections and infection-related disorders, and inborn errors of metabolism) also meet these criteria. There are ultrastructural changes believed to be specific for Reye's Syndrome which include swollen and pleomorphic mitochondria with disruption of the cristae, increase in peroxisomes and proliferation of smooth endoplasmic reticulum; glycogen depletion and absence of succinic dehydrogenase can be demonstrated histochemically (Partin 1996). However, ultrastructural analysis has not been performed in most cases of suspected Reye's Syndrome, and it is not useful as a routine diagnostic aid.

Reye's Syndrome generally presents as pernicious vomiting following a viral illness. Encephalopathy subsequently occurs, often as hyperexcitability which may progress to coma and death. However, the disease may cease progressing at any stage, and the patient may make a full recovery, although patients with severe encephalopathy may have

permanent neural damage. The fatality rate of the disease generally varies between 20-40% (De Vivo 1985, Zamula 1992, Orlowski 1984).

The viral illness which proceeds Reye's Syndrome varies. In US studies, almost all cases of Reye's Syndrome are associated with varicella or influenza A or B (>94%)(Belay et al 1999). However, in Australia, Reye's Syndrome has been associated with varicella, respiratory syncitial virus, coxsackie B, parainfluenza type 1, and even vaccination against measles or diphtheria-pertussis-tetanus (Orlowski et al 1987, Orlowski et al 1990). In the UK, like Australia, the firm association of Reye's Syndrome with influenza A and B and varicella seen in the US has not been noted, and viral illnesses associated with the illness include varicella and upper respiratory tract infections, but also gastrointestinal and other viruses (Newton and Hall 1993).

Another difference between Reye's Syndrome cases in the UK and the US is the median age of the cases. In the US, the cases are usually over 5 years of age, with a median age of 6-7 years (Belay et al 1999). In the UK, the median age of cases was 10-15 months, with the majority of cases under 5 years of age (Newton and Hall 1993). A similar situation has been observed in Australia, with a majority of cases occurring in children under the age of 5 years (Orlowski et al 1987).

These differences between Reye's Syndrome as it is commonly seen in the US, and the UK (and, apparently, Australian) cases, have led to questions about whether the term Reye's Syndrome refers to the same disease in both countries or, in fact, whether it refers to a single disease at all, or a heterogeneous group of disorders. The bulk of the literature on this subject suggests that a percentage of cases designated 'Reye's Syndrome', especially in younger children and infants, are in fact the initial presentation of inborn errors of metabolism. This theory is supported by data from the UK showing that over the last 20 years approximately 25% of children initially diagnosed with 'Reye's Syndrome' subsequently have their diagnosis altered (BPSU 2001). In Australia more than 50% of cases have been subsequently rediagnosed (Orlowski et al 1999). Not all of the remaining cases are associated with aspirin. However, this still leaves a certain number of cases of 'idiopathic Reye's Syndrome' of the classic North American pattern. The incidence of 'idiopathic Reye's Syndrome' may be greater in the US than in the UK and Australia because of the greater overall use of salicylates in the US.

The association between aspirin and Reye's Syndrome

Epidemiology studies

Despite over 20 years of study, there is still debate about the nature of the association between aspirin and Reye's Syndrome. A number of studies have been undertaken on this issue (see table below).

Ref. No	Study Type	Subjects	Methods	Results	Comments
Hall et al 1988	Case control	106 children with Reye's Syndrome cf 185 children with febrile illness admitted to hospitals	Reye's Syndrome conformed to UK definition. Cases and controls interviewed based on questionnaire for history and risk factors	72% of cases and 68% of controls were given antipyretics in the 3 weeks before admission. 59% of cases and 26% of controls received aspirin (statistically significant difference in cases and controls using aspirin in patients <5 years, but not statistically significant in patients >5 years). 25% of cases and 49% of controls received paracetamol (statistically significant difference in cases over 5 years but not statistically significant under 5 years). Mortality was 47% in cases, and median age was 23 months.	UK Study
Rennebohm et al 1985	Prospect ive	176 children with biopsy-confirmed Reye's Syndrome	Retrospective analysis of patients for connective tissue disease.	6/176 Reye's patients had connective tissue disease (4 with juvenile rheumatoid arthritis, 1 with suspected JRA and 1 with JRA-SLE overlap syndrome). All were receiving salicylates at onset of Reye's syndrome. However, only 3/6 patients with Reye's Syndrome had notable prodromal illness.	Lack of prodromal illness in 50% of cases raises questions about the diagnosis.
Starko et al 1980	Case control	7 children with Reye's Syndrome and 16 ill classmates during influenza outbreak	Cases and controls interviewed for illness characteristics and medication taken during illness (prior to hospital admission in Reye's cases)	Mean age of cases 11.3 years. 7/7 cases and 8/16 controls took salicylate-containing medication. Salicylate consumption correlated with most severe stage of Reye's syndrome in cases (r=0.67). Viral illness characteristics were similar except fever was more frequent in cases than controls.	US Study
Orlowski et al 1990	Case control	49 children with Reye's Syndrome and 94 controls admitted to 3 children's hospitals in Australia	Medical records of cases and controls reviewed for medical and medication history. CDC definition of Reye's Syndrome used.	8% of cases and 3% of controls had taken aspirin, while 24.5% of cases and 41.5% of controls had taken paracetamol. Mortality was 47% in cases.	Study criticised because medical records may not be sufficiently reliable regarding pre-admission illness.
Halpin et al 1982	Case control study	97 children with Reye's Syndrome and 156 controls matched for age, race, sex, location and type of illness.	History of illness and medication use determined by questionnaire.	97% of cases and 71% of controls used aspirin prior to onset of Reye's Syndrome (defined as onset of severe vomiting) (relative risk 11.5). Phenothiazides and trimethobenzamide were also used more frequently in cases, but not before onset of vomiting. Fever was more common in cases than controls. No relationship between aspirin dose and severity of encephalopathy. 87% of cases receiving aspirin did not exceed recommended dose.	US study. Bias possible since cases and controls not matched for incidence of fever.

Waldman et al 1982 (first study)	Case control	25 school age children with Reye's Syndrome and 46 controls matched for age race and type of illness.	Medications used after start of illness and before onset of vomiting were determined by questionnaire.	23 children had URTI, 1 had chickenpox and 1 had GIT virus as prodromal illness. 84% of cases and 52% of controls received vitamins (OR=6.01). 100% of cases and 87% of controls received some antipyretic medication. 96% of cases and 73% of controls received aspirin	US study. Two studies reported in one article. First study of cases during March-April 1980.
Waldman et al 1982 (second study)	Case control	12 school age children with Reye's Syndrome and 29 controls matched for age race and type of illness.	Medications used after start of illness and before onset of vomiting were determined by questionnaire.	10 children had URTI, 2 had chickenpox as prodromal illness. 42% of cases and 59% of controls received vitamins (OR=0.53) (not significant). 100% of cases and 44.8% of controls received aspirin. No difference b/w cases and controls for duration of illness, age of parents, mean no. of medications received and mean peak reported temperature. No relationship b/w amount of aspirin and severity of Reye's Syndrome	Second study of cases from October 1980 to April 1981. Did not confirm association with vitamins seen in first study.
Hurwitz et al 1987	Case control	27 patients with stage II or deeper Reye's Syndrome and 140 controls matched for age, race, type and timing of onset of antecedent illness	Details of illness, and medications taken were obtained by interview and questionnaire.	Antecedent illness was URTI in 93% of cases and 96% of controls, chickenpox in 4% of cases and 1% of controls, and diarrhoea in 4% of cases and 2% of controls. 96.3% of cases and 37.9% of controls received salicylates (including bismuth subsalicylate, acetylsalicylate and magnesium salicylate) (OR=40). 93% of cases and 29% of controls received aspirin (OR=26), while 19% of cases and 14% of controls received non-aspirin salicylates. Median total dose of salicylates was 74.3 mg/kg in cases and 24.5 mg/kg in controls.	Public Health Service Main Study (US)
Forsyth et al 1989	Case control	24 cases of Reye's Syndrome and 48 controls matched for age, race, time of onset and type of prodromal illness, and severity of symptoms at zero-time (time of first medication).	Medication history was obtained by interview and hospital records. Additional procedures were undertaken to examine sources of bias.	Antecedent illness was URTI in 54% of cases and 60% of controls, chickenpox in 33% of cases and 37% of controls, and other in 13% of cases and 6% of controls. 88% of cases and 17% of controls received aspirin prior to onset of Reye's (OR=35). 38% of cases and 71% of controls received paracetamol before onset of Reye's (OR=0.16). There appeared to be a relationship between total aspirin dose and risk of Reye's , although the risk was significantly increased even at the lowest dose (at <45 mg/kg OR=20; at >70 mg/kg OR=106.7).	The Yale study. Study methodology was designed to examine temporal precedence, susceptibility bias, recall bias, diagnostic bias and reporting bias. The OR for aspirin use remained high in all subset analyses testing for bias
Pinsky et al 1988	Case control	25 cases and subset of controls who had used aspirin but did not get Reye's (32 controls).	History of aspirin use by interview. Only aspirin given prior to onset of Reye's were used in analysis of cases.	There was a significant increase in mean no. of days exposed to aspirin (2.7 cf 1.9), average daily dose (25.8 mg/kg cf 15.4 mg/kg) maximum daily dose (31.8 mg/kg cf 17.3 mg/kg) and total dose over 4 days (61.6 mg/kg cf 29.6 mg/kg) in cases compared to controls. This is despite the overall severity of antecedent disease being greater in controls than cases.	Subset of PHS Main Study

Hurwitz et al 1985	Case control pilot study	30 patients with Reye's Syndrome (stage II or deeper) and 145 controls matched for age, race, and antecedent illness	Course of illness and medication history was obtained by interview.	Mean age of cases and controls was 11 years. 87% of cases had URTI and 13% had chickenpox. 93% of cases and 46% of controls received salicylates prior to onset of Reye's (OR=16.1). 27% of cases and 67% of controls received paracetamol (OR=0.22). Other medications were similar between the two groups.	PHS Pilot Study
Karger et al 1988	Case control study	24 cases of Reye's syndrome matched to 48 controls with similar severity of prodromal illness. Second control group of patients told Reye's was suspected but diagnosis later excluded	No details provided in abstract	Aspirin was used in prodromal illness in 88% of cases and 17% of controls (OR=35). Association remained significant when tested for temporal precedence (using biphasic cases only, OR=28) or diagnostic bias (stage 1 cases OR=37; stage 2 cases OR=28) or recall bias (using second group of controls OR=35).	Abstract only. Study shows aspirin association still valid when common causes of bias are controlled for.
Orlowski et al 1987	Case review	20 cases of Reye's Syndrome meeting the CDC definition	Review of medical records.	1/20 cases had aspirin use recorded. 18/20 cases had diagnosis confirmed by live biopsy. Prodromal illness was varicella, respiratory syncitial virus or coxsackie B virus in one case each, parainfluenza type 1 in 2 cases, DTP vaccination in 3 cases and measles vaccination in 1 case.	Study criticised for lack of controls and reliance on medical records (may not have sufficient detail about pre-admission medication. Lack of defined prodromal illness in 15 cases .

URTI – Upper respiratory Tract Infection
GIT – Gastrointestinal tract
OR – Odds Ratio

Without exception, the methodology of each of the studies has been criticised for sources of potential bias. Criticisms have centred on:

- Definition of onset of Reye's Syndrome: the majority of studies record medication use prior to the onset of Reye's Syndrome, defined as the first of more than one day of a pattern of symptoms including vomiting, encephalopathy etc. However, one group argues that this definition artificially hides an association between use of anti-emetics and Reye's Syndrome (since anti-emetics are given once vomiting starts, and hence are excluded from analyses since the onset of Reye's Syndrome will, by definition occur when vomiting occurs.) (Casteels-Van Daele et al 2000)
- Recall bias: it is argued that carers of patients with a serious illness (e.g. Reye's Syndrome) will be more likely to recall medication use than carers of patients with less serious illnesses (e.g. chicken pox or influenza). Also, in studies conducted after the initial suggestions of an association between aspirin and Reye's Syndrome (in 1980-1982), carers may be more likely to recall aspirin use in children diagnosed with Reye's Syndrome if they are aware of the potential association.
- Confirmation of diagnosis of Reye's Syndrome: since the definition of Reye's Syndrome is non-specific, patients with conditions mimicking Reye's Syndrome (such as inborn errors of metabolism) may have been included in the patient group, invalidating statistical analysis.
- Influence of severity of prodromal illness: It has been argued that if the prodromal illness was more severe in cases that went on to develop Reye's Syndrome, aspirin use may be more likely based on severity of symptoms. This criticism was relevant in the earlier studies on Reye's Syndrome (Wilson and Brown 1982), but most later studies matched controls and cases based on the severity of prodromal symptoms. (In the PHS Main study (Hurwitz et al 1987) cases and controls were not matched for severity of the prodromal illness, but analysis of the severity of the illness was undertaken, and severity was slightly greater in controls than in cases.) Also it could be argued that the use of paracetamol is also more likely in cases with more severe prodromal symptoms. However, it has been found that there is a negative association between paracetamol use and development of Reye's Syndrome (see table above).

These criticisms are quite valid. However, the later studies, and in particular the Public Health Service Main Study (Hurwitz et al 1987) and the study by Forsyth et al (1988) and the study by Karger et al (1989), used methodology that addresses many of these criticisms. These later studies still show a significant association between aspirin use during the prodromal illness and the development of Reye's Syndrome. It should be noted that none of the studies confirm a causal link between aspirin and Reye's Syndrome.

The Australian situation

Reye's Syndrome was named after Dr R Douglas Reye, who along with Dr Graeme Morgan and Dr Jim Baral, reported on a series of children admitted to the Royal Alexandra Hospital for Children in Sydney (now renamed The Children's Hospital, Camperdown). The original report by Reye et al (1963) did not mention aspirin use.

However, in a letter to the editor in Pediatrics in 1988, Dr Baral claimed that 11 of the 21 patients in the original study were given aspirin before the onset of their syndrome and that exposure to other sources of salicylates (such as topical creams, gels or shampoos) was possible (Baral 1988). This is in contrast to a statement by Dr Morgan in 1985 that *"We enquired into the use of medications, including aspirin, but the information we obtained did not lend itself to any likely interpretation"* (Morgan 1985).

Orlowski also reported on a series of children admitted to The Children's Hospital, Camperdown, some 10-20 years after Reye's series (Orlowski et al 1987). In this study the medical records of all 20 cases of Reye's Syndrome fitting the CDC case definition that were admitted to the hospital between 1973 and 1985 were examined. Eighteen of the 20 patients (90%) underwent liver biopsies, which were consistent with the diagnosis of Reye's Syndrome (although as noted, the biopsy results were also consistent with alternate diagnoses). Only one of the 20 patients was reported to have been administered aspirin, although this patient had a zero salicylate level when admitted to hospital after severe vomiting.

In 1990, Orlowski published another study, this time a case control study on 49 cases of Reye's Syndrome (including the original 20 cases from the 1987 report), and including 94 controls matched for age, symptoms and date seen at hospital. Unlike other case control studies on the association between Reye's Syndrome and aspirin (but similar to Orlowski's original 1984 study), this study utilised hospital medical records and patient histories to obtain data on medication given prior to and during hospitalisation (other studies generally used interviews or questionnaires of carers/parents of the patient). This study found that aspirin was administered to 8% of cases and 3% of controls (not statistically significant). The study has been criticised, however, for relying on patient histories, which, it has been suggested may not be sufficiently accurate and detailed. Medication history was confirmed by drug screens in only 15% of patients.

In 1999, Orlowski published a reassessment of 26 of the surviving Australian Reye's Syndrome cases from the 1990 study (Orlowski 1999). Eighteen of the 26 patients (69%) had subsequently been diagnosed with other conditions, most commonly inborn errors of metabolism (15/18). The most common metabolic disorder diagnosed was medium chain acyl-coenzyme-A dehydrogenase deficiency. Orlowski also reanalysed the diagnosis of all the 49 patients in the 1990 study, using medical records and more precise diagnostic criteria. Based on this reanalysis, 6 patients had probable Reye's Syndrome, 2 had possible Reye's Syndrome, 23 were unlikely to have had Reye's Syndrome, and Reye's Syndrome was excluded in 18 patients.

Mechanism of action of aspirin in Reye's Syndrome

A number of studies have been conducted to investigate how aspirin could be involved in Reye's Syndrome. However, no clear mechanism of action has been defined. It is clear from the epidemiology studies that other factors apart from viral illness and aspirin exposure are involved (perhaps genetic predisposition), since not all children with viral

illness exposed to aspirin will develop Reye's Syndrome, and some children with viral illness with no aspirin exposure appear to develop the disease.

The symptoms of Reye's Syndrome appear to be due to mitochondrial injury, at least in the liver (it is not clear whether the encephalopathy is due to primary mitochondrial injury in the brain, or is secondary to the liver injury). Although a number of mitochondrial pathways appear to be interrupted during Reye's Syndrome, inhibition of oxidative phosphorylation and fatty acid β oxidation of long chain fatty acids is thought to be primarily involved in mitochondrial failure. A number of ways in which aspirin could cause or exacerbate mitochondrial injury have been suggested.

- Aspirin has been shown to have a toxic effect on isolated rat mitochondria, including uncoupling oxidative phosphorylation, inhibiting fatty acid oxidation and depressing urea synthesis (Kwan-Sa-You 1983). These effects result in morphological changes consistent with those seen in Reye's Syndrome.
- Aspirin has been shown to compromise the immune response to viral infection by inhibiting lymphocyte transformation and interferon production (Glezen 1982).
- Aspirin has also been shown to enhance the in vitro release of tumour necrosis factor by mouse macrophages (Larrick et al 1986). Tumour necrosis factor inhibits fatty acid oxidation and produces mitochondrial damage. It is released in response to endotoxins, and endotoxin-like activity has been reported in plasma and CSF in Reye's Syndrome (Cooperstock et al 1975). Immature animals are reported to be more susceptible to the toxic effects of tumour necrosis factor (Larrick et al 1986).
- Fibroblasts from Reye's Syndrome patients have been shown to be more sensitive to inhibition of β oxidation by salicylate than control cells (Glasgow et al 1999).

It is possible that the effects of therapeutic doses of aspirin are magnified in Reye's Syndrome patients compared to normal children. One study has shown decreased aspirin esterase activity during Reye's Syndrome (Tomasova et al 1984), while another study has reported a prolonged half life for aspirin during the disease (Rodgers et al 1982). However, although some studies have suggested a connection between plasma salicylate levels or amount of aspirin ingestion and severity of incidence of Reye's Syndrome, this has not been confirmed in other studies.

Thus there are biologically plausible ways in which aspirin could be involved in the pathogenesis of Reye's Syndrome. However, the data available does not confirm a specific or causal role for aspirin. It is likely that, if aspirin is involved in Reye's Syndrome, it acts to compound injuries to an already stressed metabolism.

Incidence of Reye's Syndrome

Incidence of Reye's Syndrome in the UK

The incidence of Reye's Syndrome in the UK has been well documented through the BPSU, and is summarised in the table below (BPSU 2001).

Year (August-July)	Total reports	Diagnosis* revised	Reye's Syndrome cases	% mortality	
81/82	47	7	40	65	
82/83	69	10	59	58	
83/84	93	12	81	44	
84/85	64	8	56	57	
85/86	53[1]	13	39	56	
86/87	47	21	26	50	Aspirin warning statement
87/88	44	12	32	59	
88/89	31	13	18	50	
89/90	24[1]	8	15	47	Flu epidemic year
90/91	25	13	12	42	
91/92	23[2]	6	15	40	
92/93	21[3]	10	5	80	
93/94	20[4]	13	3	100	
94/95	17[2]	3	12	25	
95/96	18[1]	2	15	47	
96/97	7	2	5	80	
97/98	11	4	7	71	
98/99	11	4	7	29	
99/00	4	1	3	67	
00/01	3	2	0	0	

* Initial diagnosis of Reye's Syndrome subsequently revised upon further information.
1 follow-up not received for 1 case
2 follow-up not received for 2 cases
3 follow-up not received for 5 cases and 1 case did not meet case definition
4 follow-up not received for 5 cases

From 1986 until 1999, there were 17 cases (out of a total of 172 cases) of Reye's Syndrome associated with aspirin use in the UK: 7 in children under 12 years of age, and 10 in those aged 12 years and over. Therefore approximately 10% of cases were associated with aspirin use (although it is possible that more cases were associated with aspirin use that was not recorded).

Incidence of Reye's Syndrome in Australia

The Australian Institute of Health and Welfare collects data on hospital separations from all public and private hospitals in Australia. Data is available on the number of hospital separations with a principal diagnosis of Reye's Syndrome since 1993 (tabulated below).

Year	**No of cases**	**Details**
1993/94	2	Both females aged 5-9 years
1994/95	2	Both females aged >40 years
1995/96	1	Male aged 15-19 years
1996/97	0	
1997/98	1	Male aged <1 years
1998/99	1	Female 1-4 years
1999/2000		
2000/01	1	Male 20-24 years

As can be seen from the above table, there have been 8 cases of Reye's Syndrome admitted to Australian hospitals in the last 10 years (Halpin 2003, personal communication). One of the cases was aged < 1 year, 3 were in the age group 1-9 years, 3 in the age group >20 years, and only one in the age group 10-19 years. Based on these data, the regulatory change to aspirin in the UK (from *"Do not use in children under the age of 12 years"* to *"Do not use in children under the age of 16 years"*) would have had no effect in Australia over the last 10 years.

It should be noted that the Australian data do not include any cases of Reye's Syndrome that were not admitted to hospital. There is also no follow-up data on these cases, and it is not known whether any subsequently had their diagnosis changed (however, see Orlowski 1999 for changes in diagnosis for cases initially diagnosed in the 1980s).

Incidence of Reye's Syndrome in the US

The incidence of Reye's Syndrome in the US has been monitored through the Centres for Disease Control and Prevention (CDC) by the National Reye's Syndrome Surveillance System (NRSSS). The NRSSS, unlike the BPSU, is a passive surveillance system, relying on doctors to report incidents of the condition, whereas the BPSU actively questions paediatricians on a monthly basis about conditions of interest (including Reye's Syndrome). The results of the NRSSS are summarised below (Belay et al 1999).

Year (December –November)	**Number of cases reported**	
1977	Approx 450	
1978	Approx 215	
1979	Not recorded	
1980	555	Association with aspirin first suggested
1981	Approx 275	
1982	Approx 200	Advisory issued by Surgeon General
1983	Approx 190	
1984	Approx 190	
1985	Approx 100	
1986	Approx 100	Labelling of aspirin
1987	≤36	
1988	≤36	
1989	≤36	
1990	≤36	
1991	≤36	
1992	≤36	
1993	≤36	
1994	≤3	
1995	≤3	
1996	≤3	
1997	≤3	

Summary

Reye's Syndrome is a rare condition affecting children, generally during the recovery phase of a viral illness. The incidence of Reye's Syndrome has decreased over the last 20 years from a peak incidence in the late 1970s/early 1980s. Some commentators claim that the reduced incidence of Reye's cases is due to a reduction in aspirin administration to children with fever or viral symptoms. Others claim that the reduction in Reye's cases is due to more effective diagnosis of inborn errors of metabolism which may mimic the diagnostic criteria for Reye's Syndrome. The association of aspirin administration with Reye's Syndrome and even the existence of Reye's Syndrome itself, is controversial, even after 40 years of study. The cause of Reye's Syndrome is not known, but is most likely to be multifactorial, and may represent a series of insults to metabolic processes.

One view in the literature has been that many patients with Reye's Syndrome have been misdiagnosed, and actually have an inborn error of metabolism. This view of "misdiagnosis" comes about because of the definition of Reye's Syndrome, which includes the fact that there must be "no other explanation for the symptoms". Thus, once an inborn error of metabolism is detected, the cases automatically does not meet the current definition of Reye's Syndrome.

However, it seems more likely that Reye's Syndrome occurs as a result of a combination of insults (which may include exposure to salicylates and viruses, as well as other factors) in patients who already have a metabolic defect. These metabolic defects may be detected at the time of Reye's symptoms occurring, or at a later time in surviving patients, or indeed may not be detectable with current testing procedures. Thus it could be questioned whether the current definition of the disease is still appropriate, and should perhaps be modified to include patients with Reye's symptoms who do have an inborn error of metabolism. Also, it is possible that the reduction in Reye's Syndrome cases may be partially due to earlier diagnosis of some of these inborn errors of metabolism, such that effective therapy is undertaken before Reye's Syndrome occurs.

Recommendation

The available evidence suggests that while a proportion of cases meeting the definition of Reye's Syndrome are in fact other conditions (including inborn errors of metabolism, drug toxicity or others), there have still been a number of cases of "idiopathic" or "classic North American-type" Reye's Syndrome. Although individually many of the studies investigating a possible link between aspirin and Reye's Syndrome are flawed, the overall weight of evidence suggests that there is a real association between aspirin administration during the prodromal illness, and this "idiopathic" Reye's Syndrome. Whether this link is causal has not been proven.

Given the above information, the current Australian aspirin warning statement *"Consult a doctor before giving this medicine to children or teenagers with chicken pox, influenza or fever"* still seems relevant. However, given the small number of cases of Reye's

Syndrome in Australia in the last ten years, and in particular the small number of cases in the 10-19 year age group, there is no evidence to suggest that a stronger warning, such as the new UK warning "Do not give to children under the age of 16 years, unless on the advice of a doctor" is necessary on safety grounds.

In the interests of simplifying warnings on the labels of aspirin-containing products, the MEC, at it's meeting on 3 April 2003, recommended the following statements for consideration by NDPSC for inclusion in Appendix F of the SUSDP in relation to aspirin:

"*Don't use [this product/ name of the product]*

- *If you have a stomach ulcer;*
- *In the last 3 months of pregnancy*
- *If you are allergic to aspirin or anti-inflammatory medicines.*

Unless a doctor has told you to, don't use [this product/ name of the product]

- *For more than a few days at a time*
- *If you have asthma;*
- *In children under 12 years of age;*
- *If you are pregnant*."

The existing warning statement regarding Reye's syndrome could be incorporated into this new warning format by adding *"In children 12-16 years of age with or recovering from chicken pox, influenza or fever"* under the dot point relating to children under 12 years of age.

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