What dose of aspirin should be used in the initial treatment of Kawasaki disease?

SCENARIO

You are looking after a previously well child recently diagnosed with Kawasaki disease (KD). You start him on intravenous immunoglobulin (IVIG) and are about to start him on aspirin. Knowing the potential adverse effects of aspirin, you wonder whether low-dose aspirin is as effective as high-side aspirin to prevent coronary artery complications.

STRUCTURED CLINICAL QUESTION

In a child with KD (patient), is low-dose aspirin (intervention) as effective as high-dose aspirin (control) in reducing the risk of coronary artery complications (outcome) when used with IVIG.

SEARCH STRATEGY AND OUTCOME

PubMed and Medline (Ovid, 1946–present) were searched in June 2017 using the following keywords: Kawasaki AND (aspirin OR salicyl* OR ASA) AND (dose OR dosage). Results were limited to those published in English. Case reports and small case series were excluded, as were studies in which patients were not treated with IVIG and those that did not compare different aspirin doses (including a low 'anti-thrombotic' dose) within the same study. This identified 333 articles, of which six were relevant (table 1). A hand search of these publications (and those listed in table 2) revealed no additional articles.

Table 1 What dose of aspirin should be used in the initial treatment of Kawasaki disease?

Citation	Study group	Study type (level of evidence)	Outcomes	Key results	Comments
Dallaire *et al*[1] (2017)	Canada 1213 children with KD (2004–2015)	Retrospective cohort	Prevalence of CAA (*z* score≥2.5), duration of fever	*All treated with IVIG (single dose 2 g/kg)* *Paracetamol use not reported* High-dose ASA (80 mg/kg/day) (n=848) vs low-dose ASA (3–5 mg/kg/day) (n=365) New CAA: 20.5% vs 22.2%, adjusted risk difference: 0.3% (95% CI −4.5% to 5.0%) Persistent CAA (>6 weeks): 13.2% vs 12.3%, adjusted risk difference: −1.9% (−5.3% to 1.5%) Duration of fever: 7.8±3.8 days vs 7.9±2.6 days, adjusted risk difference: 0.18 days (−0.2 to 0.61 days) Follow-up: 12 months	Study concludes no difference in reduction of risk of CAA between high-dose and low-dose ASA Large study Aspirin dose based on centre guidelines and not severity of disease Variation in rescue therapy (second dose of IVIG, steroid and monoclonal antibody use, and so on)
Kim *et al*[2] (2017)	Korea 8456 children with KD	Retrospective cohort	Prevalence of CAA (*z* score≥2.5 and Japanese criteria)	*All treated with IVIG (single dose 2 g/kg)* *Paracetamol use not reported* Medium/high-dose ASA (≥30 mg/kg/day) (n=7947) vs low-dose ASA (3–5 mg/kg/day) n=509 *z*-score: 24.8% vs 18.3% (p=0.001) Japanese criteria: 19.0% vs 10.4% (p<0.001) Follow-up: 3 months	Study concludes that medium/high dose of ASA not protective against CAA Worse outcomes with high-dose ASA Not randomised, therefore more severe cases may have been given higher dose of ASA Unbalanced number of subjects
Amarilyo *et al*[3] (2017)	Israel 358 children with KD (2003–2014)	Retrospective cohort	Prevalence of CAA, length of hospital stay, fever ≥72 hours	*All treated with IVIG (single dose 2 g/kg)* *Paracetamol use not reported* High-dose ASA (80–100 mg/kg/day) (n=315) vs low-dose ASA (3–5 mg/kg/day) (n=43) New CA aneurysm: 10.2% (20/196) vs 4.2% (1/24) (p=0.34) New CA ectasia: 24.5% (48/196) vs 4.2% (1/24) (p=0.024) Equivalence tests: risk difference unlikely >3.5% Hospital stay: 7.3±4.6 days vs 5.7±2.8 days (p=0.03) Fever ≥72 hours: 9.3% vs 7% (p=0.62) Follow-up: not reported	Study concludes no difference in clinical outcome between high-dose and low-dose ASA Aspirin dose based on specific centre guidelines and not severity of disease Unbalanced number of subjects
Kuo *et al*[4] (2015)	Taiwan 851 children with KD (1999–2009)	Retrospective cohort	Prevalence of CAA, length of hospital stay, resolution of fever (<48 hours)	*All treated with IVIG (dose not reported)* *Paracetamol use not reported* Medium/high-dose ASA (>30 mg/kg/day) (n=305) vs no ASA (n=546) New CAA: 52/302 (17.2%) vs 84/546 (15.3%) (p=0.67) Length of hospital stay: 6.3±0.2 days vs 6.7±0.2 days (p=0.13) No resolution of fever: 10.2% vs 7.0% (n=38) (p=0.07) Follow-up: not reported	Study concludes no benefit of high-dose ASA on CAA formation or resolution of fever Lower Hb and impaired decrease in CRP and hepcidin in high-dose ASA group noted
Rahbarimanesh *et al*[5] (2014)	Iran 69 children with KD	Observational	Prevalence of CAA, duration of fever, length of hospital stay	*All treated with IVIG (single dose 2 g/kg)* *Paracetamol use not reported* High-dose ASA (80–100 mg/kg/day) (n=27) vs low dose ASA (3–5 mg/kg/day) (n=42) New CAA: 4% vs 5.3% (p=1.000) Duration of fever: 41.96±19.63 hours vs 46.00±50.49 hours (p=0.694) Length of hospital stay: 6.0±1.3 days vs 6.36±2.80 days (p=0.540) Follow-up: 8–10 weeks	Study concludes that high-dose ASA has no advantage over low-dose. Small study Patients allocated to low-dose aspirin group only if no coronary artery aneurysm observed
Saulsbury[6] (2002)	USA 72 children with KD (1987–2000)	Retrospective cohort	Prevalence of CAA, duration of fever	*Treated with IVIG; 400 mg/kg for 4 days (n=21) or single dose 2 g/kg (n=51)* *Paracetamol use not reported* High-dose ASA (80–100 mg/kg/day) (n=23) vs low-dose ASA (3–5 mg/kg/day) (n=46) Prevalence of CAA: 17%; all identified pretreatment No new CAA Duration of fever: 47±8 hours vs 34±5 hours (p=0.13) Follow-up: up to 8 weeks	Study concludes no difference in fever duration with different doses of ASA. Differing IVIG doses not accounted for in results

ASA, aspirin; CAA, coronary artery aneurysms; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Table 2 What dose of aspirin should be used in the initial treatment of Kawasaki disease?

Guideline	Recommended aspirin treatment (with 2 kg/day intravenous immunoglobulin single infusion)	Recommended duration of aspirin	Additional comments
American Heart Association[19] (USA, 2017)	Moderate-dose (30–50 mg/kg/day) or high-dose (80–100 mg/kg/day)	Until afebrile, then low-dose (3–5 mg/kg/day) for 6–8 weeks	Recommends continuing low-dose aspirin for patients with coronary abnormalities
Eleftheriou *et al*, Archives of Disease in Childhood[20] (UK, 2014)	Moderate-dose (30–50 mg/kg/day)	Until afebrile and inflammation subsided, then low-dose (3–5 mg/kg/day) for 6–8 weeks	Recommends continuing low-dose aspirin for patients with coronary abnormalities 'until aneurysms resolve'
Japanese Circulation Society[21] (Japan, 2014)	Low-dose (3–5 mg/kg/day) (Consider other antiplatelet drugs (dipyridamole 2–5 mg/kg/day or ticlopidine 5–7 mg/kg/day))	'About 3 months'	Recommends continuing low-dose aspirin for patients with coronary abnormalities
The Royal Children's Hospital Melbourne[22] (Australia, 2007)	Low-dose (3–5 mg/kg/day)	6–8 weeks	Consider aspirin 30 mg/kg/day for first few days, but highlights this has no additional benefit

COMMENTARY

To prevent coronary artery complications resulting from the acute inflammatory response in KD, treatment with IVIG 2 g/kg as a single infusion is recommended. In the acute phase of KD, guidelines also recommend the use of varying doses of aspirin for its anti-inflammatory and antithrombotic (table 2).

All six of the studies that met our criteria found no difference in the prevalence of coronary artery aneurysms (CAA) in patients treated with low-dose compared with high-dose aspirin.[1–6] We found no relevant randomised controlled trials. Most studies compared outcomes in patients treated with different regimens in the same institutions (physician preference[2 4 6] or reason for choice of regimen not reported[5]). The two most recent studies compared patients in institutions using different regimens over the same time period.[1 3]

The use of aspirin in the acute phase of KD dates from before the use of a single high dose of IVIG became routine, following trials showing its effectiveness.[7] Aspirin inhibits both the cyclooxygenase enzyme (COX)-1 (gastric mucosa and platelet aggregation) and COX-2 (inflammation) pathways. However, due to its considerately more selective inhibition of COX-1, larger doses are required for its anti-inflammatory (COX-2) effects.[8]

Two different high-dose 'anti-inflammatory' aspirin regimens have been used in KD. Concerns about adverse effects led to the use of a dose of 30–50 mg/kg/day (sometimes referred to as a 'moderate dose') in Europe and Japan rather than the 80–100 mg/kg/day dose used in the USA. Adverse effects of aspirin include hepatic toxicity,[9] gastritis and upper gastrointestinal bleeding,[10] sensorineural hearing loss[11] and Reye syndrome.[12] One argument for the higher dose is that therapeutic salicylate levels are difficult to achieve in the acute phase of KD due to impaired absorption from hypoalbuminaemia and increased renal excretion.[13] However, in the subacute phase, when albumin levels normalise, a larger binding capacity to unbound salicylate typically causes sudden rises in salicylate levels and associated increased risk of toxicity and adverse effects.[14]

When high-dose 'anti-inflammatory' aspirin is used in the acute phase of KD, many guidelines recommend changing to low-dose aspirin after resolution of fever for its antiplatelet effects to prevent coronary artery thrombosis during the subacute and convalescent phases.

For some time, experts have argued that high-dose 'anti-inflammatory' aspirin is not necessary in the acute phase of KD as it adds little, if any, anti-inflammatory effect over and above that provided by IVIG,[15 16] and that the lack of additional benefit does not justify exposing patients to the risk of adverse effects from high-dose aspirin. Some guidelines therefore recommend low-dose (3–5 mg/kg/day) 'anti-thrombotic' aspirin from the start to avoid the risk of adverse effects of high-dose aspirin.

The studies in our review did not report adverse effects of aspirin. However, the risk of adverse effects, including minor bleeding complications and gastric discomfort, is dose-dependent.[8 17 18]

Despite the growing evidence that the risk of using high-dose aspirin outweighs the benefit, guidelines from the UK, Japan and USA still recommend the initial use of high-dose 'anti-inflammatory' aspirin. Of note, the most recent AHA guidelines highlight there is no evidence that use of either moderate (30–50 mg/kg/day) or high-dose (80–100 mg/kg/day) aspirin reduces the risk of CAAs. Our review supports using low-dose (3–5 mg/kg/day) aspirin in the acute phase of KD.

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