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EDITORIALS

Fluoroquinolones and the aorta

Possible link with aortic pathology but the absolute risk appears very low

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Do fluoroquinolone antibiotics cause aortic pathology? In a linked article (doi:10.1136/bmj.k499), Pasternak and colleagues report a population based study of the association between outpatient treatment with fluoroquinolones (principally ciprofloxacin and norfloxacin) and aortic aneurysms and dissection.[1] Compared with patients prescribed amoxicillin, those prescribed fluoroquinolones had a 66% increase in the 60 day risk of aortic aneurysm or dissection (hazard ratio 1.66, 95% confidence interval 1.12 to 2.46).

This is not the first study to explore this question, but from a methodological perspective it is arguably the strongest. Unlike in earlier studies,[2 3] Pasternak and colleagues used an active comparator (amoxicillin). This makes obvious sense, because patients treated with antibiotics are systematically different from those who are not. Other strengths included a large sample size, comprehensive prescription data, and well balanced characteristics between groups at baseline, owing to propensity score based matching.

But do fluoroquinolones actually cause aortic pathology? It is sometimes said that observational studies cannot prove a causal association between an exposure and an outcome, but this is not entirely true (we have no randomised trials of smoking and lung cancer, for example). What is true is that imputing cause and effect from observational studies involves making a judgment, and that judgment is often hard. This is one of those times.

When evaluating whether an association is causal, it is helpful to reflect on the nine criteria put forth by Austin Bradford Hill in 1965: biological plausibility, consistency, coherence, specificity, strength of association, gradient, experiment, analogy, and temporality.[4] This involves considering a pattern of information, rather than following an algorithm, or tabulating a score. The various factors are not weighted equally, but the more that are fulfilled, the more likely an association is to be causal.

In this instance, biological plausibility seems fairly evident: the aorta is rich in collagen, and the ability of fluoroquinolones to alter the integrity of collagen is well known, even if the mechanisms are poorly understood.[5] The criterion of consistency is likewise met, with two related studies from other jurisdictions yielding comparable findings.[2 3] Subtly different from plausibility is the criterion of coherence, the most obtuse of the Bradford Hill criteria. Coherence is best understood by asking "How much of what I already know do I have to sacrifice to accept this association as causal?" To me, the idea that fluoroquinolones might cause aortic pathology seems fully compatible with existing knowledge about the drugs and their off-target effects.[5]

The criterion of specificity, which holds that one putative cause should yield one specific effect, is the least useful of the Bradford Hill criteria. (Does anyone believe that smoking causes only lung cancer?) However, a variant is sometimes useful in observational studies: falsification analysis, which can strengthen causal inference by documenting the absence of an association where none is expected. In the study by Pasternak and colleagues, the finding of no difference in all cause mortality fulfils this criterion, albeit not optimally.

Two notable criteria not met are strength of association and gradient. A strong association is not necessarily causal, but it is more likely to have a causal component than a modest one. In some books, a hazard ratio of 1.66 barely qualifies as modest. This in itself is not an argument against causation; it is simply less compelling. Gradient (sometimes termed dose-response) was not examined. Whether higher doses or longer durations of fluoroquinolone treatment show stronger associations with aortic pathology is unknown; this would require a different approach and a dataset with considerably more than 64 outcome events.

Of the remaining criteria, the experiment criterion is not evaluable—there will never be a human trial to examine whether fluoroquinolones cause aortic pathology. In contrast, the criterion of analogy holds. Reasonably good evidence exists for a causal association between fluoroquinolones and disorders of tendons[6 7] and the retina,[8 9] both of which are rich in collagen.

One final criterion warrants special attention. Temporality is Bradford Hill's only essential criterion, and in the study by Pasternak and colleagues would seem to be met by design. But it is curious that the survival curves for fluoroquinolones and amoxicillin diverge almost immediately. Does it seem plausible that the anatomy of the aorta could be seriously compromised by fluoroquinolones in a matter of days, as the authors postulate, or is another explanation at play? The separation of curves is so acute that it raises the possibility of differential outcome

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ascertainment, as might occur if patients receiving fluoroquinolones underwent abdominal imaging more often than those receiving amoxicillin. Given that fluoroquinolones are more likely to be used in complex urinary tract infections, this seems at least possible.

On balance, this study strengthens the link between fluoroquinolones and aortic disease, but causality remains far from proved. Even if it is the case, the absolute risk is very low—at 82 extra cases of aneurysm or dissection within 60 days for every million treatment episodes—and the advice remains the same: prescribe antibiotics judiciously.

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