REPORT

Does Aspirin help or damage the liver?

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Abstract

Aspirin is one of the most widely used medicines in the world and has been on the market for over a century. Therefore, it is surprising that little solid research has been done regarding the effects of aspirin on the liver. If anything, you can find a few studies from the 1970s. At that time, aspirin was described as damaging to the liver by quite some authors. But since the turn of the millennium, studies have suddenly appeared that attribute a liver-protective effect to aspirin. We have investigated this contradiction and found a tipping point effect of high clinical relevance.

Situation

As the active ingredient in one of the world's most widely used medicines, acetylsalicylic acid is marketed as one of the best researched substances of all. Since its launch under the famous trade name ASPIRIN in 1899 in Germany, acetylsalicylic acid use has spread around the globe. People all over the world use aspirin, which has had a firm place in private homes, hospitals and doctors' offices for more than 100 years to treat pain, fever and inflammation. Aspirin is a fascinating medical substance, it is amazingly versatile and always good for a surprise. In low doses (80 to 100mg/day) it is an excellent and underestimated anti-thrombotic, in medium doses (600 to 1500mg/day) it acts as an analgesic and reduces fever, in the high dose range (1500 to 3000mg/day) it is a highly effective non-steroidal anti-inflammatory medication (COX inhibitor) whose properties are superior to those of many more modern substances.[16] These dose differences are not only associated with varying effects, but also with dissimilar safety profiles. We reviewed the relevant literature and found a common thread in a jumble of studies and research findings. Due to the extremely broad spectrum of effects and side effects, we looked specifically at the impact of aspirin on the liver.

Studies and Data

That the effect of acetylsalicylic acid on the liver became a topic of relevance not before the 1970s is strongly related to the fact that two aspects, which are taken for granted today, were not available until forty to fifty years ago: the possibility for rapid and cheap measurements of liver enzymes and cholestatic parameters as part of a standard laboratory examination, and sonography. If the laboratory and sonography technology as we know it today would have existed back then many medical drugs would never have been approved. The standard until the 1970s and 1980s was to palpate, look for signs of jaundice and, if in doubt, simply perform a blind biopsy - hoping to have hit the right liver segment.[1,4,6] The impression that we have more "liver patients" today is therefore probably an artifact caused in large part by our modern detection instruments. Whether it is beneficial to public health to have permanent laboratory follow-up checks of the liver function and to allow every moderately trained general practitioner to perform sonography of the liver is an important question, but one that goes beyond the scope of this paper. If one is completely honest, four things have really brought progress to hepatology: the extremely successful and safe vaccination against hepatitis B, the possibility of curing hepatitis C with a drug within three months, imaging by MRI since about 2005, and contrast sonography at hospitals that specialized in this field. The benefits of all other "advances" can and should be debated. Thus it came about that two phenomena collided in the 1970s. First, the still frequent use of aspirin in excess doses (up to three times the upper limit of today) as an anti-inflammatory, and second, the possibility of easily and quickly detecting silent liver dysfunction with fast and cheap laboratory test. The fact that the lively interest in aspirin’s impact on the liver ceased in the 1980s has to do with the replacement of acetylsalicylic acid as an anti-inflammatory in insanely high doses by more modern drugs.[10] However, it can by no means be claimed with certainty that this progress has also brought more help for most patients. Today, aspirin is only rarely used as an anti-inflammatory, analgesic or antipyretic outside some traditional markets like western Europe, but has embarked on a new career as an anti-thrombotic agent in the low-dose range: a classic example of how a once troublesome side effect has been redefined as a desired main effect. The switch to other NSAIDs such as ibuprofen, naproxen, and diclofenac, as well as selective COX2 inhibitors, may also be looked at critically.[10] Be that as it may, aspirin is used today mainly as an inhibitor of platelet aggregation, i.e., to protect

against heart attacks or strokes. In this low-dose range (80 to 100mg/day), aspirin has now proven to be beneficial to the liver.[13-15] However, studies with anti-inflammatory doses from the 1970s clearly indicate toxic liver damage from aspirin. So what is true, can both completely opposite findings be correct at the same time?[1,13,14,15]

Apparently, acetylsalicylic acid, the active ingredient in aspirin, has two faces with respect to the liver, and the plasma level seems to be the determining factor.[1,13-15] The question that arises is whether the change is linear with respect to the effect profile on the liver? Based on the data reviewed, the answer to this is a relative 'no'. Rather, there seems to be a tipping point (or range) at which this liver-friendly medical drug becomes a liver-harming substance. Since aspirin is still in high demand in some markets in medium doses for pain, and it still plays a less widespread but nevertheless important role as an anti-inflammatory in the treatment of non-specific, inflammatory diseases, the question arises: at which dosage is the tipping point to be found? We are not aware of any current studies dealing with this question, even after intensive research. Therefore, we checked the most reliable data from the sixties, seventies and early eighties and came across surprisingly consistent data which we are sharing with this report.

Tipping Points

We focused our selection of studies mainly on those that reported self-collected data. Unfortunately, none of them included healthy adults. In the 1970s, only patients (mostly children) with rheumatic diseases were the test subjects. After this period, research interest largely came to a standstill. Nevertheless, the quality of the selected works, measured by the standard of science of that era, is good and still useful today. The following data are the threshold values above which a highly significant increase in transaminases was measured by the respective studies. We have disregarded all those surveys that only report external data. It is all the more remarkable that all studies that are to be taken seriously came to more or less the same results:

Study	***Concentrations associated with liver injury***
Zimmermann (1981)	*>15-25mg/dL*
Russel et al. (1971)	*>27mg/100ml*
Rich & Johnson (1973)	*>20-25mg/dL*
Kanada et al. (1978)	*>25mg/100ml*
Schaller et al. (1978)	*>30mg/dL*
Bernstein et al. (1977)	*>15mg/100ml*
Babb (1978)	*>25mg/100ml*
Boss (1978)	*>20mg/dL*
Teoh & Farrell (2003)	*>24mg/dL*

Discussion

Considering the side effect profile of other non-steroidal anti-inflammatory drugs and its considerable performance, aspirin will remain part of medicine and also of self-medication in the high-dose range (1000 to 3000mg per day).[16] In this respect, it is both surprising and irksome that there are no robust new studies with a correspondingly robust design regarding the influence of acetylsalicylic acid on the liver. More than a century may justifiably be considered a sufficient time for such an endeavor. Thus, it remains only to go by the old data, which were well and solidly collected, but in a rather special group of people: mainly children, patients with arthritis, SLE and connective tissue disorders. Moreover, these patients received doses in the extreme range of 3000mg to 10000mg (3 to 10g) per day, although apparently the dose itself seems to be less critical than the concentration of acetylsalicylic acid in the blood. This in turn is only quite loosely related to the dose taken, since gender, body weight, height, muscle mass, genetic dispositions, absorption disorders, etc. have a considerable influence on the concentration of the active substance in a patient's plasma.[1-9] For incomprehensible reasons, these influencing factors were not surveyed in any study that seemed relevant to us. Even a layman would understand that it makes a difference whether a man with 110kg body weight takes 3000mg/day aspirin or this amount is given to little girl with 40kg of body weight. Therefore, and because of the risk of Reye Syndrome, aspirin is no longer given to children. The risk of people with pre-existing liver or other organ disorders remains unresearched for the time being.[10] We can only assume that there is no highly dramatic correlation, since otherwise it would have been as noticeable as the liver-destroying effect of a slightly too high dose of paracetamol/acetaminophen.

Nevertheless, considerably significant findings can be derived from the old data available. First of all it seems plausible that liver damage from acetylsalicylic acid is relatively unlikely at concentrations below 25mg/dL in a relatively healthy adult. who takes aspirin quite regularly. However, this repeatedly mentioned value should rather be understood as a range from 15 to 30mg/dL. The tipping point is thus likely to be within this range. Furthermore, not only the increases of the SGOT value are remarkable, but also the rapid resolution with drug discontinuation or dose reduction. Hepatic injury due to aspirin seems to be a slowly developing cumulative phenomenon requiring days or weeks to develop, characterized by a diffuse liver cell injury which is rarely severe in degree.[1,3,5,8,9,13,14,15] Nevertheless, it must again be emphasized that neither the mechanism of injury is understood to date nor are contradiction-free biopsy results available.

What is more, recent studies have attributed an antifibrotic (liver protecting) effect to aspirin in the case of the epidemically widespread nonalcoholic fatty liver disease (NAFLD).[13-15] Even more remarkably, Jiang and colleagues (2016) found stable SGOT values in chronic aspirin users, whereas this transaminase increased significantly (albeit undramatically) in ibuprofen users. This is highly interesting in that it is the value which responded most strikingly (in a bad way) in the studies from the 1970s. Unfortunately, the authors did not specify the doses taken by the patients studied or the plasma levels of aspirin, but referred to long-term use in the low-dose range for stroke and myocardial infarction prophylaxis. The daily dose would then have to be 80 to 100 mg. In this respect, the comparison with ibuprofen is misleading, since ibuprofen is not used in a low-dose regimen. Despite these weaknesses in the study design, new studies support the finding that low-dose aspirin could be beneficial for the liver, especially in patients with non-alcoholic fatty liver disease (NAFLD).[12,14] Permanent severe damage to the liver caused by acetylsalicylic acid does not seem to be a common phenomenon[1] in healthy adults[10], other than paracetamol/acetaminophen which slightly too high doses can lead to death due to fulminant necrosis of

the liver cells depleted of glutathione.[17] Moreover, until the 1980s, children with autoimmune diseases were treated with daily aspirin doses of 3000 to 9000mg.[1-9] This is now as inconceivable as it is prohibited by most regulatory agencies. Concentrations below 20mg/dL seem to be well tolerated by most healthy adults, although one questionable paper from Korea[11] is challenging the concept of a safe low-dose aspirin use in regard to the liver. However, this paper is of poor quality and raises more questions than it provides answers.

The European Union's Medicines Agency (EMA) allows the OTC sale of acetylsalicylic acid without prescription up to a maximum daily dose of 3000mg to adults. Whereby the full range of action (inhibition of platelet aggregation, pain relief, fever reduction and anti-inflammatory effects) is usually achieved at 1000 to 1500mg per day. Unfortunately, no measured values, rather common sense suggests that this permitted dose should not be a problem when the children who were the test subjects in the studies of the 1970s often reached a serum concentrations of >20mg/dL at doses between 3000 and 9000mg/day. In this respect, both the ban on aspirin for children (also because of the risk of Reye syndrome), which is now in force, and the permitted daily dose of a maximum of 3000mg for adults seems to be plausible, even if unnecessarily high.

Conclusion

Considering the multiple side effects of alternative medications, theoretical effects on the liver should not be a contraindication to the use of acetylsalicylic acid in the currently recommended dose range.[10,13] This is especially true if the dosage is so low that the desired effect is achieved, but the upper daily dose limit is not reached. In 2021, no physician in his right mind would prescribe the megadoses of aspirin between 3000 and 9000 mg per day that were administered fifty years ago even to particularly sensitive children. In high-risk patients and in patients taking aspirin daily at doses greater than 300 to 500 mg/day or frequently greater than 1000 to 1500 mg/day, any primary care physician may occasionally measure liver function values at his discretion and based on knowledge of the patient. Individual vulnerabilities will play a role, as will the BMI and other contributing factors. This should be left to the judgment of a responsible physician. A general warning, as is the case with paracetamol/acetaminophen because of the narrow therapeutic range of this drug, would only lead to unnecessarily poor compliance with acetylsalicylic acid. However, it remains incomprehensible why reality does not match the PR claim of the most well-known aspirin manufacturer that aspirin would be the best studied drug in the world. This is definitely not the case. Our work confirms once again that aspirin is a very versatile, important and effective drug, but definitely not a feel-good product without side effects. Instead of investing money in advertising, this fascinating active ingredient should finally be tested again after more than 100 years in use, as it would be in an approval process with the standards of 2021.

Conflicts of Interest

None.

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