Paracetamol Intake and Hematologic Malignancies

Subjects: Hematology

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Hematologic malignancies are a heterogeneous group of diseases of diverse incidence, prognosis, and etiology that cause 1.3 million cases and more than 700,000 deaths every year worldwide. These malignancies show a stable trend in the last decades, but an increased incidence is observed for myeloma in women.

paracetamol hematologic neoplasms meta-analysis

1. Overview

Hematologic malignancies cause more than half a million deaths every year worldwide. Analgesics were suggested as chemopreventive agents for several cancers but so far, results from individual studies about the relationship between paracetamol (acetaminophen) use and hematologic malignancies are conflicting. Therefore, we decided to perform a systematic review and meta-analysis. We retrieved studies published in any language by systematically searching Medline, Embase, Conference Proceedings Citation Index, Open Access Theses and Dissertations, and the five regional bibliographic databases of the World Health Organization until December 2020. Pooled odds ratios (OR) and their 95% confidence intervals (CI) were calculated according to the inverse of their variances. We performed separate analyses by histologic type. We also evaluated publication bias and assessed quality. A total of 17 study units met our inclusion criteria. The results show an association of hematologic malignancies with any paracetamol intake (OR 1.49, 95% CI 1.23–1.80) and with high paracetamol intake (OR 1.77, 95% CI 1.45–2.16). By subtype, risk was higher for multiple myeloma (OR 2.13, 95% CI 1.54–2.94) for any use and OR 3.16, 95% CI 1.96–5.10 for high intake, while risk was lower and non-significant for non-Hodgkin lymphoma. This meta-analysis provides evidence that paracetamol intake may be associated with hematologic malignancies and suggests that a dose–response effect is plausible. These results are unlikely to be due to publication bias or low quality of studies. Future research should focus on assessing the dose–response relationship.

2. Hematologic Malignancies

Hematologic malignancies are a heterogeneous group of diseases of diverse incidence, prognosis, and etiology that cause 1.3 million cases and more than 700,000 deaths every year worldwide [1]. These malignancies show a stable trend in the last decades, but an increased incidence is observed for myeloma in women [2].

Analgesics, mostly aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) were proposed as chemopreventive agents in cancers of several anatomic locations, including colon and breast, due to their cyclooxygenase (COX) prostaglandin inhibition [3][4]. Prostaglandins are known to inhibit apoptosis, promote angiogenesis and increase tumor cell proliferation [5]. Paracetamol (or acetaminophen) is a widely used non-NSAID analgesic that has a weak COX-inhibition effect [6]. Its action is essentially focused on COX-2 inhibition, while that of NSAIDs is mainly due to COX-1 inhibition. It is the major metabolite of phenacetin, an analgesic cataloged as carcinogenic by the International Agency for Research on Cancer (IARC) in 1987 and withdrawn from the market in most countries [7]. Both potential carcinogenic and chemopreventive effects of paracetamol have raised considerable interest in the last two decades [8][9]. In 1999, a report by the IARC found “inadequate evidence” of carcinogenicity for paracetamol both in human and animal studies, meaning that available data are insufficient to permit a conclusion regarding carcinogenicity [10].

Several epidemiological studies have examined the relation between paracetamol and hematologic malignancies. However, while some studies showed increased risk, others failed to do so [11]. Moreover, publication bias could have possibly distorted the global association between paracetamol and hematologic cancer [12]. Because of the considerable consumption of paracetamol worldwide, any association with increased or decreased risk of cancer may have important public health implications. Indeed, in the US, more than 600 over-the-counter and prescription medicines contain paracetamol [13], and in France, about half of the population uses this medicine [14].

The non-conclusive evidence of a relation between paracetamol and hematologic malignancies led us to conduct a meta-analysis of the studies published on the subject. This meta-analysis was registered in the PROSPERO database (ID: CRD42021245056).

3. Discussion

Our results show that paracetamol users are more likely to be diagnosed with hematologic malignancies. This association, observed in leukemia, multiple myeloma and lymphoma at large but not in non-Hodgkin lymphoma, is more pronounced for high intakes, both when all studies are taken together and when the analysis is performed by subgroup. As the studies included in this meta-analysis did not provide exact doses of paracetamol but, instead, simply a number of tablets consumed per day the dosage of which is unknown, we were not able to carry out a refined dose–response analysis. In particular, we could not compute effect measures for intakes >4 g/day, considered as a limit for toxicity. Cohort and case-control studies yielded similar results. Studies with low bias potential showed higher estimates than those with high bias potential. The effect observed is then unlikely to be due to a low quality of studies.

Several mechanisms could explain the association of paracetamol with hematologic malignancies: first, in vitro and in vivo studies have related paracetamol use to decreased DNA repair, and have shown that paracetamol may play the role of a co-mutagen [15]; second, the paracetamol metabolite N-acetyl-p-benzoquinone imine was shown to be a DNA topoisomerase II poison which was associated with secondary leukemia [16][17]. In addition, some experimental studies suggest that paracetamol is genotoxic to the bone marrow and could increase the risk of

leukemia [18]; third, laboratory evidence showed that paracetamol increases NF-κB induction and affects IL-6 transcription. Both mechanisms possibly play a major role in the myeloma disease process. Chronic exposure to paracetamol may dysregulate these mechanisms [19]. However, one should bear in mind that subtypes of hematologic malignancies are etiologically heterogeneous. Furthermore, several methods are used to classify hematologic cancers by subtypes.

Our meta-analysis has some limitations. As data were not available in the original studies, we could not take into account possible interactions of paracetamol with other drugs, essentially opioid analgesics such as hydrocodone, a combination which is frequently dispensed in the US [20]. Furthermore, as explained above, due to the lack of data in the individual studies no detailed dose–response analysis was possible, besides that regarding high intake. We are aware that the assessment of consumption as any intake/high intake represents but a suboptimal way to measure the quantity of paracetamol ingested.

It is remarkable that, in several studies included in this meta-analysis, there was no mention of the time supposedly elapsed from intake of paracetamol to occurrence of the malignancy [21][22][23][24][25][26][27]. In other studies, the time excluded from follow-up, during which the occurrence of the event is impossible (“immortal” time) may have been too short [28][29].

Also, residual confounding may have distorted our results, as in any meta-analysis of observational studies. Although we are not aware of any genetic polymorphism that could play the role of confounder of the relation between paracetamol and hematologic cancer, it is possible that such a factor exists. As a matter of fact, recent studies discovered that a polymorphism of the COX-2 gene was a confounder of the NSAIDs–breast cancer relationship [30]. However, the existence of an unidentified factor, of genetic nature or else, associated with both exposure to paracetamol and hematologic malignancies, which could explain a high proportion of the observed effect, is unlikely. Even if this unidentified factor could double the risk of malignancy among subjects exposed to it (OR confounder-disease = 2) and, simultaneously, this factor happened to be twice more prevalent among subjects exposed to paracetamol than among non-exposed subjects (OR confounder-exposure = 2), the adjusted OR of the paracetamol–hematologic cancer relationship would still be 1.32 for any intake and 1.59 for high intake (assuming one-third of people are exposed to this unknown factor) [31]. Furthermore, our analysis of fully adjusted studies yielded a higher risk of malignancies than that of studies with incomplete adjustment.

Another limitation is the fact that paracetamol is particularly prone to “confounding by indication”, a kind of bias frequent in observational studies of drug exposure. This implies that the presence of some nonspecific symptoms (such as headaches or bone pain), that could be, in fact, early manifestations of the malignancy, could lead to intake of paracetamol, thus exaggerating its association with malignancies diagnosed subsequently. Furthermore, regular and heavy consumers of analgesics tend to have a higher level of comorbidity that can easily disturb the relationship between this and future health outcomes, if not properly accounted for. This kind of bias is more frequent in studies which use prevalent cases, or in studies of mortality without previous follow-up [32]. However, in the studies included in our meta-analysis, most case-control studies used incident cases, and the large majority adjusted for consumption previous to the diagnosis or to the first symptoms. Moreover, cohort studies, a design

less prone to this kind of bias, as well as studies with low risk of bias showed a larger effect of paracetamol. The sensitivity analysis, performed after exclusion of the mortality cohort by Lipworth et al. [22], did not modify the results except for a decrease in heterogeneity.

Furthermore, there is some evidence of publication bias for the “any intake” group. This means that some relevant studies may not have been published and, therefore, were not included in the meta-analysis, which could potentially affect the results. This issue has been mentioned by previous narrative reviews [12]. In our meta-analysis, we did not include any limitation on language, year, or type of study. It is then unlikely that the search could miss relevant published studies. Also, the funnel plot shows a lack of studies at the right-hand side, i.e., studies that would present an increased risk of malignancies. This suggests that, in any case, our results are conservative, and the possible publication bias should go in the direction of an even more increased effect. Moreover, both the trim-and-fill method and the pooled estimates with extreme assumptions did not reverse our conclusions.

Previous studies show that 23% of the US population and 50% of the French population use paracetamol [14][33]. On the basis of these prevalences of use and our results, assuming that the associations we observed were of causal nature, we estimate that between 10% and 20% of hematologic malignancies may be attributable to paracetamol among users [34].

4. Conclusions

The magnitude of the associations, the consistency of the results through different settings, and the existence of a mechanism that gives biologic plausibility to the relationship, provide evidence that paracetamol may be associated with hematologic malignancies.

The fact that paracetamol is widely available over-the-counter in the majority of countries supposes a major public health issue that needs to be further investigated. More than measuring in a precise fashion the excess risk of hematologic malignancies among paracetamol users, our meta-analysis should be considered as a call for methodologically rigorous epidemiologic studies that would provide a definitive answer on the relation of paracetamol and hematologic cancers. In addition to assessing the dose–response relationship, these future studies should provide hypotheses on the lag time between exposure to paracetamol and occurrence of hematologic malignancies necessary for a causal relationship.

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