Should methionine be added to every paracetamol tablet?

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Abstract
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Should methionine be added to every paracetamol tablet?

Paracetamol is commonly used for self poisoning, and the costs of treating the resulting liver failure in the few who develop it are high. The morbidity could be avoided by adding methionine to paracetamol tablets, but this would mean that the millions of people who take paracetamol responsibly would have to take methionine unnecessarily. Alison Jones and colleagues and Edward Krenzelok debate the issue.

No: The risks are not well enough known

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Each year in the United Kingdom roughly 2600 million tablets of paracetamol are sold over the counter and 600 million supplied on prescription (Paracetamol Information Centre Study, November 1993). Paracetamol overdose is common in many parts of the world.

In studies in Britain and America paracetamol was the commonest drug used in overdose, being taken in about 48% of overdoses in Oxford and 5% in America. Clinicians in general, and those working in liver transplant units in particular, are increasingly aware of the problems raised by the liver damage caused by paracetamol, and pressure is growing to find some preventive measure. Adding the antidote methionine to paracetamol tablets is attractive, but because most people who take overdoses act impulsively it would have to be added to every formulation to be of maximum value. The critical issue then is whether the vast numbers of responsible users of paracetamol should have no choice but to take it with methionine in order to protect the minority who take overdoses.

**Cost of paracetamol poisoning**

Overdose of paracetamol causes hepatotoxicity ranging from mild, asymptomatic derangement of liver function to fulminant hepatic failure and death. Official statistics considerably overestimate the number of deaths from paracetamol poisoning. Thus in 1990, of 547 deaths attributed to paracetamol in England and Wales, only 150 were substantiated after review.

The official returns include people who never reach hospital and who are more likely to have died from the effects of other drugs ingested concomitantly (especially dextropropoxyphene). Few conscious people would suffer the symptoms of severe hepatic injury for even a few days without seeking medical attention.

Of 667 patients who received a liver transplant in the United Kingdom in 1995, only 29 had liver failure caused by paracetamol poisoning (R Bates, Scottish Liver Transplant Unit, personal communication). Such patients are commonly young and the need for transplantation is invariably urgent. They therefore receive top priority for donor organs and reduce those available to other patients.

At any one time, around 100 patients are waiting for elective liver transplantation in Britain, and as the average survival time for advanced cirrhosis is less than one year, some will die while waiting. In the United States admissions to hospital and days off sick related to paracetamol overdosage have been estimated to cost $86.9 million/year.

The cost of paracetamol poisoning is therefore high but must be considered in the context of the drug’s therapeutic benefits, the enormous quantity sold, and the advantages of its availability over the counter.

Would a paracetamol and methionine formulation prevent liver damage?

There have been no reports of overdose with paracetamol and methionine combinations in humans and therefore no hard evidence exists that liver damage from overdose has a sound biochemical rationale.

Excessive production of N-acetyl-p-benzoquinoneimine, a toxic metabolite of paracetamol, depletes hepatic glutathione concentrations leading to covalent binding and destruction of hepatic cells. Methionine protected against such damage in animal studies and in clinical trials (when given to patients who admitted taking a paracetamol overdose). It probably acts by promoting synthesis of glutathione.

The period between taking the overdose and administration of the methionine is critical since the hepatocytes must be intact in order to convert the methionine to cysteine for the synthesis of glutathione. In clinical practice it prevented significant liver damage.
and leucocytosis after 8 g of methionine daily for four days and changes in serum pH and potassium with increased urinary calcium excretion after 13.9 g daily for five days. Schizophrenic patients given 10-20 g daily for two weeks developed functional psychoses and single doses of 8 g precipitated hepatic encephalopathy in patients with cirrhosis.

Methionine metabolites are involved in the transformation of malignant cells. In addition, in vitro and in vivo studies in animals with tumours have shown that restriction of methionine intake specifically blocks division and metastasis of tumour cells. The possibility that long term increased intake of methionine could promote carcinogenesis has not been evaluated.

Methionine is metabolised to homocysteine and vice versa in a methylation cycle, and raised plasma homocysteine concentrations have been associated with peripheral vascular disease, ischaemic heart disease, and stroke; coagulation abnormalities; vascular injury; endothelial dysfunction; and vascular smooth muscle proliferation. Oral administration of methionine (200 mg/kg/day) to rats for 14 days increased the concentrations of homocysteine in serum and produced angiotoxic effects similar to atherosclerosis.

Reservations about combined preparations

Only one paracetamol and methionine combination preparation remains available in the United Kingdom: Paradote (500 mg paracetamol, 100 mg methionine). Pameton (500 mg paracetamol, 250 mg methionine) has been voluntarily removed from the market because of safety concerns. Similar preparations are not currently available in the rest of Europe or in the United States. Both cost four to six times more than proprietary paracetamol, and one tastes unpleasant. Although methionine has few side effects, it causes nausea and headache in some cases. The methionine in both formulations is the dl racemate, but it is unlikely that the dl form can be converted to the l form in vivo.

No data are available on the relative efficacy of the two forms of methionine in protecting the liver after paracetamol overdose in humans, but if only l-methionine is bioavailable it would be better to use this than a racemic mixture. d-Methionine prevented acute paracetamol hepatotoxicity in rats, but unlike humans, rats use d-methionine efficiently.

The issue of dose

Another issue is the dose of methionine. As weight ratios of methionine to paracetamol of as low as 10% protected rats from hepatotoxicity, the ratios used in Paradote (20%) and particularly the former Pameton (50%) may be overgenerous. The effective prophylactic antitodal dose of methionine in humans remains to be established. The safety of long term ingestion of methionine in addition to that already in the diet is important.

Studies of dietary supplementation in healthy people have shown reduced serum folate concentrations if given orally or intravenously within 10 hours of paracetamol overdose.
The paracetamol era began in 1886 when it was recognised that acetanilide had analgesic and antipyrretic properties. What went unrecognised for years was that acetanilide’s therapeutic properties were secondary to paracetamol. The toxicity of acetanilide’s other metabolite, aniline, was unacceptable, and various derivatives were synthesised to find a suitable alternative with analgesic and antipyrretic properties. Phenacetin was soon recognised as a viable alternative, and paracetamol was first used for medicinal purposes in 1893. However, it did not become popular until 1949. In 1995 paracetamol sales in the United States were roughly $965m (personal communication, IMS America, Plymouth Meeting, PA 19462-1048).

Poison or remedy?
To paraphrase the Swiss philosopher and physician Paracelsus: only the dose differentiates a poison from a remedy. Paracetamol is not an exception to this rule. At therapeutic doses paracetamol is relatively benign, but when it is ingested in excessive amounts endogenous hepatic glutathione is depleted and the toxic metabolite of paracetamol (N-acetyl-p-benzoquinoneimine) binds covalently with hepatocytes causing cellular death and hepatic necrosis. In 1961-2 paracetamol exposure was the most common incident reported to American poison centres, accounting for 5.5% of all exposures. Furthermore, paracetamol overdose was the leading cause of death from poisoning, being implicated in 9.9% of such deaths.

All poisonings are not reported to poison information centres, and it is estimated that full reporting would lead to about 58% more exposures. Extrapolating this to the paracetamol data for 1991-5, the number of poisonings would increase from 518 205 to 1 233 821 and the number of deaths from 355 to 845. An additional 4250 people would suffer life threatening sequelae. The number of people treated in a healthcare facility would rise from 130 968 patients to 311 829. These data represent the United States alone, and the world figures would be staggering. Paracetamol poisoning is clearly a serious problem—what are the solutions?

Antidotes
The glutathione surrogate or precursors cysteamine, methionine and N-acetylcycteine have been used successfully to treat paracetamol poisoning. Currently in the United States patients are given oral N-acetylcycteine, and other countries use intravenous N-acetylcysteine (which is not approved in America). N-Acetylcysteine is especially effective when used soon after the overdose. Since early intervention is important the idea of incorporating a prophylactic antidote, such as methionine, into each paracetamol tablet was proposed in 1974. As a precedent, naloxone was already incorporated into pentazocine tablets as a deterrent to abuse. However, adding methionine was dismissed as costly and discriminating against the majority of people who use paracetamol properly. Given the large numbers of fatal and life threatening exposures to paracetamol, is it time to reconsider incorporation of methionine into every paracetamol tablet?

Financial justification
The financial implications of hospital treatment, liver transplantation, and death make adding methionine very appealing. The mean cost of hospital treatment...
Adding methionine to paracetamol makes it more expensive, but would the benefits justify the expense?

for paracetamol poisoning in America is about $8700/case (£5400). If half of the patients who were treated in a healthcare facility for paracetamol poisoning were admitted to hospital over $1.36bn would have been spent on their care. The number of liver transplants related to paracetamol poisoning is unknown, but the costs range from $165 000 to $927 000, excluding the lifelong expenses for antirejection drugs and other treatment. If each lost life was valued at $3.6m, paracetamol related deaths would have cost over $3bn.

The expenses incurred for only five years make a compelling argument for adding methionine to each paracetamol tablet. But do the financial advantages outweigh the disadvantages?

Disadvantages

Cost is promoted as the main disincentive. Methionine costs around £7.50/kg. If 250 mg methionine were added to each paracetamol tablet the cost of 100 tablets would increase by £1.90. However, methionine would be considerably less expensive if purchased in large quantities. Nevertheless, this cost seems a small price to pay considering the enormous financial burden associated with overdoses.

There are contentions that methionine may be mutagenic and carcinogenic. Since some people take paracetamol daily this could have serious implications. When sodium chloride and sodium nitrite were incubated with meat, methionine caused a mutation in Salmonella typhimurium TA 1535. However, this does not imply that methionine is a universal mutagen. Methionine has prevented the progression of hepatic cancer in rats. In contrast, methionine deprivation is thought to have some antitumour activity. Excessive methionine in the diet may induce atherosclerosis in lagomorphs and reduce serum folate concentrations in humans. Clearly, the arguments for and against adding methionine can be rationalised by using selective research. There is still much to be learnt about methionine and its role in many physiological processes.

Limited possibilities

What are the alternatives to methionine? In developed countries N-acetylcysteine is abundantly available and relatively inexpensive, although the associated hospital costs add considerably to the price of treatment. In these countries it seems better to treat paracetamol poisoning reactively rather than expose the majority of people to an unnecessary and more costly substance. However, my experience in developing nations has shown that N-acetylcysteine and methionine are not universally available. If a paracetamol-methionine combination can be produced economically it may be ethical to encourage its use in developing nations where the introduction of paracetamol often precedes the availability of N-acetylcysteine and where there are insufficient financial resources to justify the expense of treatment.

How to read a paper
Assessing the methodological quality of published papers
Trisha Greenhalgh

Before changing your practice in the light of a published research paper, you should decide whether the methods used were valid. This article considers five essential questions that should form the basis of your decision.

**Question 1: Was the study original?**

Only a tiny proportion of medical research breaks entirely new ground, and an equally tiny proportion repeats exactly the steps of previous workers. The vast majority of research studies will tell us, at best, that a particular hypothesis is slightly more or less likely to be correct than it was before we added our piece to the wider jigsaw. Hence, it may be perfectly valid to do a study which is, on the face of it, "unoriginal." Indeed, the whole science of meta-analysis depends on the literature containing more than one study that has addressed a question in much the same way.

The practical question to ask, then, about a new piece of research is not "Has anyone ever done a similar study?" but "Does this new research add to the literature in any way?" For example:

- Is this study bigger, continued for longer, or otherwise more substantial than the previous one(s)?
- Is the methodology of this study any more rigorous (in particular, does it address any specific methodological criticisms of previous studies)?
- Will the numerical results of this study add significantly to a meta-analysis of previous studies?
- Is the population that was studied different in any way (has the study looked at different ages, sex, or ethnic groups than previous studies)?
- Is the clinical issue addressed of sufficient importance, and is there sufficient doubt in the minds of the public or key decision makers, to make new evidence "politically" desirable even when it is not strictly scientifically necessary?

**Question 2: Whom is the study about?**

Before assuming that the results of a paper are applicable to your own practice, ask yourself the following questions:

- *How were the subjects recruited?* If you wanted to do a questionnaire survey of the views of users of the hospital casualty department, you could recruit respondents by advertising in the local newspaper. However, this method would be a good example of recruitment bias since the sample you obtain would be skewed in favour of users who were highly motivated and liked to read newspapers. You would, of course, be better to issue a questionnaire to every user (or to a 1 in 10 sample of users) who turned up on a particular day.
- *Who was excluded from the study?* Many trials in Britain and North America routinely exclude patients with coexisting illness, those who do not speak English, those taking certain other medication, and those who are illiterate. This approach may be scientifically "clean," but since clinical trial results will be used to guide practice in relation to wider patient groups it is not necessarily logical. The results of pharmacokinetic studies of new drugs in 23 year old healthy male volunteers will clearly not be applicable to the average elderly woman.
- *Who was included in the study?* For example, a randomised controlled trial may be restricted to patients with moderate or severe forms of a disease such as heart failure—a policy which could lead to false conclusions about the treatment of mild heart failure. This has important practical implications when clinical trials performed on hospital outpatients are used to dictate "best practice" in primary care, where the spectrum of disease is generally milder.
- *Were the subjects studied in "real life" circumstances?* For example, were they admitted to hospital purely for observation? Did they receive lengthy and detailed explanations of the potential benefits of the intervention? Were they given the telephone number of a key research worker? Did the company that funded the research provide new equipment which would not be available to the ordinary clinician? These factors would not necessarily invalidate the study itself, but they may cast doubt on the applicability of its findings to your own practice.

**Question 3: Was the design of the study sensible?**

Although the terminology of research trial design can be forbidding, much of what is grandly termed "critical appraisal" is plain common sense. I usually start with two fundamental questions:

- *What specific intervention or other manoeuvre was being considered, and what was it being compared with?* It is tempting to take published statements at face value, but remember that authors frequently misrepresent (usu-
ally subconsciously rather than deliberately) what they actually did, and they overestimate its originality and potential importance. The examples in the box use hypothetical statements, but they are all based on similar mistakes seen in print.

**Question 4: Was systematic bias avoided or minimised?**

Systematic bias is defined as anything that erroneously influences the conclusions about groups and distorts comparisons. Whether the design of a study is a randomised controlled trial, a non-randomised comparative trial, a cohort study, or a case-control study, the aim should be for the groups being compared to be as similar as possible except for the particular difference being examined. They should, as far as possible, receive the same explanations, have the same contacts with health professionals, and be assessed the same number of times by using the same outcome measures. Different study designs call for different steps to reduce systematic bias:

**Randomised controlled trials**

In a randomised controlled trial, systematic bias is (in theory) avoided by selecting a sample of participants from a particular population and allocating them randomly to the different groups. Figure 1 summarises sources of bias to check for.
Non-randomised controlled clinical trials

I recently chaired a seminar in which a multidisciplinary group of students from the medical, nursing, pharmacy, and allied professions were presenting the results of several in house research studies. All but one of the studies presented were of comparative, but non-randomised, design—that is, one group of patients (say, hospital outpatients with asthma) had received one intervention (say, an educational leaflet) while another group (say, patients attending GP surgeries with asthma) had received another intervention (say, group educational sessions). I was surprised how many of the presenters believed that their study was, or was equivalent to, a randomised controlled trial. In other words, these commendably enthusiastic and committed young researchers were blind to the most obvious bias of all: they were comparing two groups which had inherent, self selected differences even before the intervention was applied (as well as having all the additional potential sources of bias of randomised controlled trials).

As a general rule, if the paper you are looking at is a non-randomised controlled clinical trial, you must use your common sense to decide if the baseline differences between the intervention and control groups are likely to have been so great as to invalidate any differences ascribed to the effects of the intervention. This is, in fact, almost always the case.6

Cohort studies

The selection of a comparable control group is one of the most difficult decisions facing the authors of an observational (cohort or case-control) study. Few, if any, cohort studies, for example, succeed in identifying two groups of subjects who are equal in age, sex mix, socioeconomic status, presence of coexisting illness, and so on, with the single difference being their exposure to the agent being studied. In practice, much of the “controlling” in cohort studies occurs at the analysis stage, where complex statistical adjustment is made for baseline differences in key variables. Unless this is done adequately, statistical tests of probability and confidence intervals will be dangerously misleading.

This problem is illustrated by the various cohort studies on the risks and benefits of alcohol, which have consistently found a “J shaped” relation between alcohol intake and mortality. The best outcome (in terms of premature death) lies with the cohort who are moderate drinkers.5 The question of whether “teetotallers” (a group that includes people who have been ordered to give up alcohol on health grounds, health faddists, religious fundamentalists, and liars, as well as those who are in all other respects comparable with the group of moderate drinkers) have a genuinely increased risk of heart disease, or whether the J shape can be explained by confounding factors, has occupied epidemiologists for years.8

Case-control studies

In case-control studies (in which the experiences of individuals with and without a particular disease are analysed retrospectively to identify putative causative events), the process that is most open to bias is not the assessment of outcome, but the diagnosis of “caseness” and the decision as to when the individual became a case.

A good example of this occurred a few years ago when a legal action was brought against the manufacturers of the whooping cough (pertussis) vaccine, which was alleged to have caused neurological damage in a number of infants.9 In the court hearing, the judge ruled that misclassification of three brain damaged infants as “cases” rather than controls led to the overestimation of the harm attributable to whooping cough vaccine by a factor of three.9

Question 5: Was assessment “blind”? 

Even the most rigorous attempt to achieve a comparable control group will be wasted effort if the people who assess outcome (for example, those who judge whether someone is still clinically in heart failure, or who say whether an x ray is “improved” from last time) know which group the patient they are assessing was allocated to. If, for example, I knew that a patient had been randomised to an active drug to lower blood pressure rather than to a placebo, I might be more likely to recheck a reading which was surprisingly high. This is an example of performance bias, which, along with other pitfalls for the unblinded assessor, is listed in figure 1.

Question 6: Were preliminary statistical questions dealt with? 

Three important numbers can often be found in the methods section of a paper: the size of the sample; the duration of follow up; and the completeness of follow up.

Sample size

In the words of statistician Douglas Altman, a trial should be big enough to have a high chance of detecting, as statistically significant, a worthwhile effect if it exists, and thus to be reasonably sure that no benefit exists if it is not found in the trial.10 To calculate sample size, the clinician must decide two things.

The first is what level of difference between the two groups would constitute a clinically significant effect. Note that this may not be the same as a statistically sig-
significant effect. You could administer a new drug which lowered blood pressure by around 10 mm Hg, and the effect would be a significant lowering of the chances of developing stroke (odds of less than 1 in 20 that the reduced incidence occurred by chance).11 However, in some patients, this may correspond to a clinical reduction in risk of only 1 in 850 patient years—a difference which many patients would classify as not worth the effort of taking the tablets. Secondly, the clinician must decide the mean and the standard deviation of the principal outcome variable.

Using a statistical nomogram,10 the authors can then, before the trial begins, work out how large a sample they will need in order to have a moderate, high, or very high chance of detecting a true difference between the groups—the power of the study. It is common for studies to stipulate a power of between 80% and 90%. Underpowered studies are ubiquitous, usually because the authors found it harder than they anticipated to recruit their subjects. Such studies typically lead to a type II or β error—the erroneous conclusion that an intervention has no effect. (In contrast, the rarer type I or α error is the conclusion that a difference is significant when in fact it is due to sampling error.)

Duration of follow up
Even if the sample size was adequate, a study must continue long enough for the effect of the intervention to be reflected in the outcome variable. A study looking at the effect of a new painkiller on the degree of postoperative pain may only need a follow up period of 48 hours. On the other hand, in a study of the effect of nutritional supplementation in the preschool years on final adult height, follow up should be measured in decades.

Completeness of follow up
Subjects who withdraw from (“drop out of”) research studies are less likely to have taken their tablets as directed, more likely to have missed their interim checkups, and more likely to have experienced side effects when taking medication, than those who do not withdraw.11 The reasons why patients withdraw from clinical trials include the following:

- Incorrect entry of patient into trial (that is, researcher discovers during the trial that the patient should not have been randomised in the first place because he or she did not fulfil the entry criteria);
- Suspected adverse reaction to the trial drug. Note that the “adverse reaction” rate in the intervention group should always be compared with that in patients given placebo. Inert tablets bring people out in a rash surprisingly frequently;
- Loss of patient motivation;
- Withdrawal by clinician for clinical reasons (such as concurrent illness or pregnancy);
- Loss to follow up (patient moves away, etc);
- Death.

Simply ignoring everyone who has withdrawn from a clinical trial will bias the results, usually in favour of the intervention. It is, therefore, standard practice to analyse the results of comparative studies on an intention to treat basis.13 This means that all data on patients originally allocated to the intervention arm of the study—including those who withdrew before the trial finished, those who did not take their tablets, and even those who subsequently received the control intervention for whatever reason—should be analysed along with data on the patients who followed the protocol throughout. Conversely, withdrawals from the placebo arm of the study should be analysed with those who faithfully took their placebo.

In a few situations, intention to treat analysis is not used. The most common is the efficacy analysis, which is to explain the effects of the intervention itself, and is therefore of the treatment actually received. But even if the subjects in an efficacy analysis are part of a randomised controlled trial, for the purposes of the analysis they effectively constitute a cohort study.

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