Paracetamol, ibuprofen, or a combination of both drugs against knee pain: an excellent new randomised clinical trial answers old questions and suggests new therapeutic recommendations

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At first glance, the title of the article published by Doherty et al[1] **(see page 1534)** does not promise much. Who would be interested in reading an investigation comparing two old well-known analgesics with each other or combinations of both? At a second glance, however, this cautious and excellent long-term study reveals many new and important findings which should be the basis for reconsideration of the treatment of musculoskeletal conditions with over-the-counter (OTC) analgesics. It may turn out that many of our widely-held beliefs and assumptions are wrong and that the recommendation for our patients needs to be changed.

Doherty et al investigate whether the combination of ibuprofen and paracetamol is better than the active components alone. To answer this question the authors compared the efficacy and safety of paracetamol and ibuprofen as well as that of two combinations of these drugs in community-derived patients aged >40 years with chronic knee pain. In a randomised, double-blind, four-arm parallel-group active controlled trial, the short-term (day 10) and long-term (week 13) benefits and side effects of four different therapeutic regimens were analysed:

1. ibuprofen (400 mg three times a day);
2. paracetamol (1000 mg three times a day);
3. one fixed-dose combination tablet (ibuprofen 200 mg/paracetamol 500 mg (low-dose) three times a day);
4. two fixed-dose combination tablets (ibuprofen 400 mg/paracetamol 1000 mg (high-dose) three times a day).

In their four cohorts which included almost 900 participants the authors found that, at the first study end point (day 10), the high-dose combination was superior to paracetamol alone for pain relief, but was not superior to ibuprofen alone (table 1). At the second study end point (week 13), significantly more participants taking one or two combination tablets rated their treatment as excellent/good compared with paracetamol alone; ibuprofen alone was better than paracetamol and not statistically inferior to the high-dose combination.

Adverse events were comparable between all groups, but numerically higher in the groups receiving combination tablets. Interestingly, the incidence of dyspepsia or diarrhoea was not lower in the paracetamol only group (as would have been expected by common wisdom). On the other hand, it is not surprising to find that the ibuprofen only group had no signs of liver toxicity in contrast to all three paracetamol groups. After 13 weeks a fall in haemoglobin (>1 g/dl) occurred more frequently in patients taking a combination than in those on monotherapy with paracetamol or ibuprofen. The blood loss in the high-dose combination group was significantly higher than in all the other groups and reached clinically relevant proportions.

The authors conclude that the analgesic regimen of an ibuprofen/paracetamol combination confers modest short-term benefits for knee pain/osteoarthrosis and

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Table: Effects of paracetamol (P) and ibuprofen (I) alone or in combination (P + I) in long term therapy of OA of the knee

Effects[1]	P 3 x 1g/d	I 3x 0.4g/d	P (3 x 0.5g) + I (3 x 0.2g/d)	P (3 x 1g) + I (3 x 0.4g/d)	Comments
Pain reduction (mm reduction from baseline, day 10)[2]	10.1	13.3	12.8	15.0 **[3] vs P	P is inferior to I or P + I
Patients' global assessment (% rating good or excellent)	38.1	54.6 *vs P	53.9	61.4 **vs P	combinations are not superior to I
AEs, any drug related[4,5]	27.5	21.0 p<?	28.8	30.8	P alone or in combination causes more AEs than I
Dyspepsia (day 10)[4]	5.0	6.3	11.7	6.3	P alone or in combination causes as many dyspepsia or diarrhea as I
Diarrhoea (day 10)[4]	4.5	1.8	1.8	6.7	
ALAT[3,4,5]	3.1	0.0	1.0	3.4	P alone or in combination causes impairment of liver function
γ GT (> 2x normal limit)[4]	6.7	0.5	3.5	3.4	
Hb ↓ (> 1 g from baseline, day 10)[4,5]	7.3	11.3	10.8	17.5 p<0.01**	P and I cause blood loss; P + I (high dose) enhance blood loss
> 1 g at study endpoint[4,5]	20.3	19.6	24.1	38.4 p<0.01**	Blood loss due to P + I reaches clinically relevant proportions with time
> 2 g at study endpoint[4,5]	0.9	0.9	1.8	6.9 p<?	The effect of P + I appears more than additive (p<?)

[1] If not stated otherwise: at day 10
[2] As measured with a 10 cm VAS
[3] * p<0.05; ** p<0.01
[4] results as % of cohort
[5] Alanine transferase (alanine transaminase; % of patients showing > 2x normal limit)

that patients taking paracetamol (3 g/day) may have similar degrees of blood loss to those taking ibuprofen (1200 mg/day). In addition, patients on the high-dose combination appear to have a higher blood loss than those on ibuprofen alone.

However, there is more to be considered. The important results are summarised in table 1.

Concerning pain relief, the data clearly show that (1) paracetamol 1000 mg three times a day does not provide satisfactory pain relief in the majority of patients; (2) neither the high- nor the low-dose combination of ibuprofen with paracetamol is superior to ibuprofen alone; and (3) ibuprofen alone or combined with paracetamol is superior to paracetamol alone.

The results described here should be used as an argument to avoid the combination of different cyclo-oxygenase (COX) inhibitors. Interestingly, several studies published during the past few years have shown that paracetamol is an inhibitor of peripheral COX enzymes.[2–4] In one of these studies preferential COX-2 inhibition was reported in volunteers receiving 1000 mg paracetamol.[3] However, this effect was short-lived and did not result in the prolonged 80% inhibition of COX-2 that is necessary for pain relief,[5] thus explaining the only moderate analgesic action of paracetamol compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs). More relevant, however, these data strongly imply that overdosing two COX-2 inhibitors—in this case ibuprofen and paracetamol—is not expected to enhance analgesia given that a plateau is reached with a sufficient dose of either drug. In the present case, sufficient COX-2 inhibition had most likely already been achieved with ibuprofen 400 mg three times a day.

More important (although not statistically significant) are the reported unwanted drug effects: the proportion of drug-related adverse effects is actually higher in the treatment groups exposed to paracetamol/ibuprofen combinations. Dyspepsia and diarrhoea were observed with paracetamol and all combinations at least as frequently as dyspepsia following ibuprofen alone. Signs of liver toxicity (increased alanine aminotransferase and γ-glutamyltransferase) were seen in all groups receiving paracetamol. Paracetamol administration accompanies (causes?) and enhances blood loss. Remarkably, the blood loss increases with time and the dose of paracetamol, with or without ibuprofen.

The finding that patients on the high-dose combination lost more blood than those on ibuprofen alone is in agreement with a previously published retrospective cohort study of older patients who reported an increased risk of gastrointestinal bleeding with a combination of a traditional NSAID and paracetamol compared with either agent alone.[6] The authors explained this finding by the additional COX-1 inhibition by paracetamol, which is plausible in view of data showing that paracetamol augments the inhibitory action of diclofenac on platelet aggregation.[7]

In conclusion, it is very gratifying to see that this study which investigates the therapeutic value of combining two non-aspirin COX inhibitors is published at all. We doubt that another study of comparable size, cost and quality will be performed in the near future, certainly not supported by a drug company. The results indicate that we should reconsider using a combination of analgesics and also the use of paracetamol alone, as it is not sufficiently effective yet causes many unwanted effects including dyspepsia, diarrhoea, and gastrointestinal blood loss. In line with this notion, studies published during the past few years have shown that paracetamol increases blood pressure when taken for short or prolonged periods[8–10] and augments the risk of major cardiovascular events when administered at high frequency or dose.[11] Moreover, there is no mechanistic justification for the combination of paracetamol with another COX-2 inhibitor: the enzyme responsible for the formation of algesic prostaglandin E_2 can only be blocked once. Two blockers cannot achieve more effects than one blocker! The analgesic action increases only marginally (if at all), but the unwanted drug effects increase substantially.

On the basis of this study, one wonders why combinations of analgesics of the type described and investigated here should remain on the OTC market. Obviously there is no scientific evidence that either claim—higher efficacy and/or less toxicity—can be substantiated—rather, the contrary is true.

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