The pharmacokinetics of tenidap sodium: introduction

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Tenidap is a novel compound which combines some of the properties of both traditional first-line (or non-steroidal anti-inflammatory drugs [NSAIDs]) and second-line (disease-modifying anti-rheumatic drugs [DMARDs]) agents. The successful clinical use of any drug depends upon the optimum balance between beneficial and adverse effects. Many anti-rheumatic drugs have a poor reputation for safety and one of the challenges for the pharmaceutical industry is to produce safe and effective anti-rheumatic drugs. Knowledge of the drug’s pharmacokinetics and drug interactions is crucial in achieving this balance. This is especially so with a new drug where, of necessity, clinical experience is limited. In this supplement, a collection of papers describing the pharmacokinetics and potential drug interactions of tenidap are brought together and between them they should contribute significantly to the safer and more effective use of tenidap in clinical practice.

Four papers in this supplement investigate factors which might affect the pharmacokinetics of tenidap. Caldwell et al. found that single dose pharmacokinetics of tenidap in both osteoarthritis and rheumatoid arthritis were not affected significantly by age or sex of the subject. Gardner et al. found that, following multiple dosing, the intrinsic clearance of tenidap was increased and steady state was achieved by the eleventh day of dosing. Thus, although of interest, as tenidap has been shown to be effective following multiple dosing in patients with rheumatoid arthritis, this observation is unlikely to have any clinical relevance.

Two studies have looked at the effect of other drugs or food on the pharmacokinetics of tenidap. Coates & Mesure found that taking tenidap with food delayed absorption but had no statistically significant effect on Cmax or AUC. Co-administration of antacid (Maalox®: aluminium hydroxide 1.8 g/magnesium hydroxide 1.2 g), however, resulted in a statistically significant reduction in AUC and Cmax as well as a reduction in tmax. Again, however, although statistically significant, none of these effects are of a magnitude likely to be of clinical relevance. Tenidap is extensively metabolised, and although it is unknown whether this is via the hepatic P450 microsomal enzyme system, it is prudent to investigate whether drugs that alter the activity of these enzymes have any effect on tenidap metabolism. Wilner & Gardner investigated the effect of cimetidine on the clearance of tenidap in healthy volunteers. They found a minimal increase in AUC(0,24h) at steady state following cimetidine administration which just achieved statistical significance although, once more, the magnitude of the effect is unlikely to be of clinical relevance.

The bulk of papers in this supplement investigate the effect of tenidap on the pharmacokinetics and pharmacodynamics of other drugs. Apseloff et al. found that tenidap, in common with NSAIDs, reduces the renal clearance and increases the mean steady state concentration of lithium in healthy volunteers. The magnitude of this effect may well be significant, particularly in view of the low therapeutic ratio of lithium, and it is recommended that serum concentrations of lithium are carefully monitored if a patient on lithium commences tenidap, and also if the tenidap dose is changed or the drug withdrawn. The same group also investigated the effect of tenidap on the pharmacodynamics and plasma protein binding of warfarin in healthy volunteers. They found a small but significant increase in the prothrombin time AUC(0,120h) in the volunteers receiving tenidap compared with those receiving placebo. Although the increase in prothrombin time appears small and unlikely to be of clinical significance, warfarin was given to healthy volunteers as a single dose and the effect may be more significant in patients with cardiovascular and perhaps other pathology taking long term warfarin. Thus the authors’ recommendations are that, if tenidap is co-administered with warfarin, additional monitoring of the prothrombin time is undertaken.

Blum et al. examined the effect of tenidap on phenytoin pharmacokinetics. They found a significant (25%) increase in the free phenytoin fraction measured ex vivo following regular dosing with tenidap. This was not accompanied by a reduction in the total phenytoin concentration in vivo as might have been expected if free phenytoin clearance had remained unaltered. This implied reduction in free clearance of phenytoin may result from phenytoin’s zero order kinetics rather than a direct effect on tenidap on phenytoin clearance. The net result, irrespective of mechanism, would be an increase in unbound concentrations of phenytoin which, especially in view of phenytoin’s low therapeutic ratio, could lead to significant phenytoin toxicity if co-administered with tenidap. Thus, if these drugs are co-administered, phenytoin plasma concentration should be monitored carefully. If possible, free phenytoin should be measured. However, this is not available in many centres and if total concentration is monitored it must be remembered that the effect of increasing the unbound fraction is to reduce the ‘target range’ of total phenytoin quite considerably. Of importance to the mechanism of the interaction between phenytoin and tenidap is the finding, also published in
this supplement by Wilner & Gardner, that tenidap does not affect the handling of tolbutamide which is metabolised by the same P450 enzyme as phenytoin. Dewland et al. report no significant effect of prolonged tenidap administration on the pharmacokinetics of digoxin in healthy volunteers. Again there is a caveat that the results cannot be extrapolated to predict the safety of the two drugs in combination in patients with, perhaps, multi-organ pathology, although they give no ground to suppose that the co-administration of the two drugs is contraindicated. Coates & Mesure also investigated the effect of tenidap on a low dose combined oral contraceptive (Microgynon 30®) in healthy premenopausal females. There was no effect of tenidap on any of the pharmacokinetic parameters for either ethinyloestradiol or levonorgestrel.

The final interaction studies were both by Rapeport et al. The first of these investigated the effect of tenidap on the antihypertensive effect of thiazide diuretics and the second the effect of tenidap on the antihypertensive effect of ACE inhibitors. Both studies were carried out in patients with mild to moderate hypertension and both showed a statistically significant but relatively small increase in blood pressure with tenidap compared with placebo. Thus it is recommended that for patients with hypertension receiving either thiazide diuretics or ACE inhibitors who are concurrently administered tenidap, blood pressure should be carefully monitored.

The final paper does not relate to either pharmacokinetics or drug interactions but to an investigation of the photosensitising potential of tenidap. The use of a provocative test such as this to identify adverse effects is important when it is available as it has obvious advantages over the usual observational techniques for identifying adverse effects. Using this technique, Ferguson & Leeming were unable to demonstrate a photosensitising effect of tenidap at the doses used.

The series of papers in this supplement have failed to show a clinically significant effect of various factors on tenidap pharmacokinetics although both antacids and cimetidine had some statistically significant effect (in opposite directions). There is no information in this supplement on the effect of renal or hepatic impairment on tenidap elimination and clearly information on this is important and it is intended to publish this at a later date.

Tenidap affects the pharmacokinetics of lithium and phenytoin to an extent which is likely to have clinical significance in at least some patients and careful monitoring is important when it is co-administered with either of these drugs. Although clinically significant interactions were not seen with warfarin or digoxin both studies were carried out in healthy volunteers and caution is needed in extrapolating these results to the patient groups likely to be receiving therapy. Such a caveat does not need to be extended to interpreting the lack of interaction with the combined low dose oral contraceptive. Interactions, possibly pharmacodynamic, are seen with both ACE inhibitors and thiazide diuretics, resulting in reduced anti-hypertensive efficacy of both groups and, again, awareness of this interaction is important to allow closer blood pressure monitoring. It is clear from these studies that, despite their differences, the interaction profiles of NSAIDs and tenidap are similar.

The studies published here therefore contribute significantly to our knowledge and understanding of how to use tenidap safely and hopefully make an important contribution to achieving the optimum balance between beneficial and adverse effects.