

THE EFFECTS OF GASTRIC EMPTYING AND DISINTEGRATION RATE ON THE ABSORPTION OF PANADOL ACTIFAST® TABLETS

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INTRODUCTION

Panadol Actifast® is a new rapidly absorbed paracetamol tablet containing sodium bicarbonate. Pharmacokinetic studies in man have shown a significantly shorter t_{max} (both fed and fasted states) and a significantly higher C_{max} (fasted state) for Panadol Actifast® compared to conventional paracetamol tablets (Panadol®), following oral dosing, Grattan et al, (2000), Rostami-Hodgson et al, (2002). To investigate the hypothesis that this is due to enhanced gastric emptying and dissolution/disintegration mechanisms, a combined scintigraphy and pharmacokinetic study was conducted.

METHODS

STUDY DESIGN

This was a single centre, randomised, four-way, within subject study in 11 healthy, non-smoking males and females aged 21 to 36 years (mean 27.0 +/- 4.6).

5mg lactose, radiolabelled with 2MBq ^{99m}Tc -DTPA, was incorporated into each tablet during manufacture to facilitate scintigraphic imaging. For the purposes of this trial no film coating was applied to the tablets. In vitro dissolution tests were conducted to assess paracetamol release rate from each formulation, using the USP II paddle apparatus at 30 rpm in 0.5M HCl.

In each study arm, a two tablet dose of one formulation was dosed in either fed or fasted conditions as shown in Table 1, in accordance with the study randomisation.

Study Arm	Formulation	Conditions
A	Panadol®	Fasted state
B	Panadol®	Fed state
C	Panadol Actifast®	Fasted state
D	Panadol Actifast®	Fed state

Table 1. Dosing schedule.

IMAGING SCHEDULE

Following dosing the subjects were imaged in a reclining position with the gamma camera. Anterior static acquisitions of 30-second duration were collected every 5 minutes for a period of 30 minutes, then every 15 minutes to 2 hours. After this time the volunteers were imaged in a standing position, every 30 minutes to 4 hours then hourly to 10 hours.

SCINTIGRAPHIC ANALYSIS

Images were analysed using the WebLink® image analysis program. Tablet disintegration times and gastric emptying times were determined by two independent trained operators.

PHARMACOKINETICS

Blood samples were withdrawn at pre-defined intervals. They were then centrifuged and the serum fraction was removed and stored at -20°C. Serum paracetamol levels were measured using a validated UV-HPLC assay.

RESULTS

IN VIVO TABLET DISINTEGRATION

Table 2 shows the mean tablet disintegration times. Wilcoxon Matched Pairs Test was used to compare parameters from different treatments. The mean disintegration times are suggestive of faster disintegration for Panadol Actifast® than for Panadol® in both the fed and fasted states, but the difference is significant in the fed state only ($p=0.0053$). Similarly, mean disintegration times for both formulations are suggestive of faster disintegration in the fasted state compared to the fed state, but the differences are not significant.

	Mean	SD	Median
Panadol Actifast® Fasted	10.2	9.3	7.5
Panadol Actifast® Fed	14.3	11.0	12.5
Panadol® Fasted	22.5	12.8	17.5
Panadol® Fed	46.4	38.0	37.5

Table 2. In vivo disintegration times

GASTRIC EMPTYING

Fig. 1 shows mean gastric emptying curves for the four study arms. In the fasted state, Panadol Actifast® tablets emptied from the stomach faster than Panadol®, but the differences were not significant. However, in two subjects, emptying of Panadol Actifast® was dramatically retarded. This may be due to the fact that both subjects were menstruating at this stage of the study. The menstrual cycle has been linked to changes in gastric emptying patterns, Wald et al, (1981). If data from these two subjects is excluded, onset of emptying, time to 50% gastric emptying (t_{50}) and time to 90% gastric emptying (t_{90}) were all significantly faster for Panadol Actifast® than for Panadol® ($p=0.0448$, 0.0112 and 0.0042, respectively).

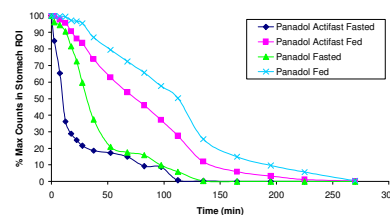


Fig. 1: Mean gastric emptying curves (n=11)

In the fed state onset of emptying, t_{50} and t_{90} were all faster for Panadol Actifast® than for Panadol®, although the differences were not significant. Since the meal will dominate the emptying process under these conditions, this is to be expected and is consistent with the findings of the recent pharmacokinetic study, Rostami-Hodgson et al (2002). Representative scintigraphic images are shown in fig. 2.

Panadol® Fasted Panadol Actifast® Fasted

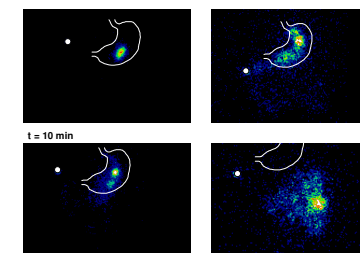


Fig. 2: Representative scintigraphic images (subject 7) showing gastric emptying of both formulations in the fasted state

ABSORPTION RATE

AUC_{0-60} minutes correlated with t_{50} for all treatment arms, and with t_{90} for all treatment arms except Panadol Actifast® fed (Table 3). This indicates that the extent of early absorption (and by extension the absorption rate) was dependent on the rate of gastric emptying.

	$AUC_{0-60} v t_{50}$	$AUC_{0-60} v t_{90}$
Panadol Actifast® Fasted	0.0011*	0.0011*
Panadol Actifast® Fed	0.0017*	0.3195
Panadol® Fasted	0.0013*	0.0003*
Panadol® Fed	0.0201*	0.0276*

Table 2. Correlation of early AUC with gastric emptying times

CONCLUSION

These results confirm faster gastric emptying and disintegration of Panadol Actifast® tablets compared to conventional Panadol® tablets. While these effects exist in both the fed and fasted states, the differences in gastric emptying are more pronounced in the fasted state and the differences in disintegration are more pronounced in the fed state. It would seem that a combination of these factors is responsible for the shorter t_{max} and higher C_{max} that have previously been shown in a larger study.

REFERENCES

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