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Short communication

A new anticancer agent (LY186641) interferes with creatinine assay

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Summary. The administration of a diarylsulfonylurea, LY186641, which is presently undergoing a multicentric phase I clinical trial as an anticancer agent, produces major analytical interference with commonly used creatinine analysis techniques. We confirm that this interference is caused by a metabolite rather than the parent compound and propose an alternative, interference-free method.

Introduction

In collaboration with Lilly Research Center Limited (Windlesham, Surrey, UK), we started a phase I clinical trial of LY186641, which is a member of a novel class of antitumor drugs, the diarylsulfonylureas [1]. The schedule used in our institute consists of a single oral dose given daily for 2 weeks. A weekly protocol has reported positive results in an ovarian carcinoma patient at the recent American Society of Clinical Oncology (ASCO) meeting in New Orleans [3]. Therefore, LY186641 is likely to undergo a phase II clinical trial in the near future.

As originally indicated by Dr. R. R. Swain (Lilly Research Laboratories, Indianapolis, personal communication), we observed significant interference of up to 300% with creatinemia determinations during the course of our phase I trial. Two major metabolites of LY186641 have thus far been identified; they display either a keto or hydroxy substitution on the indane ring. Thus, three compounds were screened to determine which is responsible for the reported interference.

Results

Creatinine assays are routinely carried out in our laboratory using a modified Jaffé method on a Beckman ASTRA 8. On this analyzer, an apparent elevation in creatininemia appeared 4 h after the first ingestion of the drug and, depending on the dose given, was still observed 4–7 days after the completion of the treatment (Fig. 1).

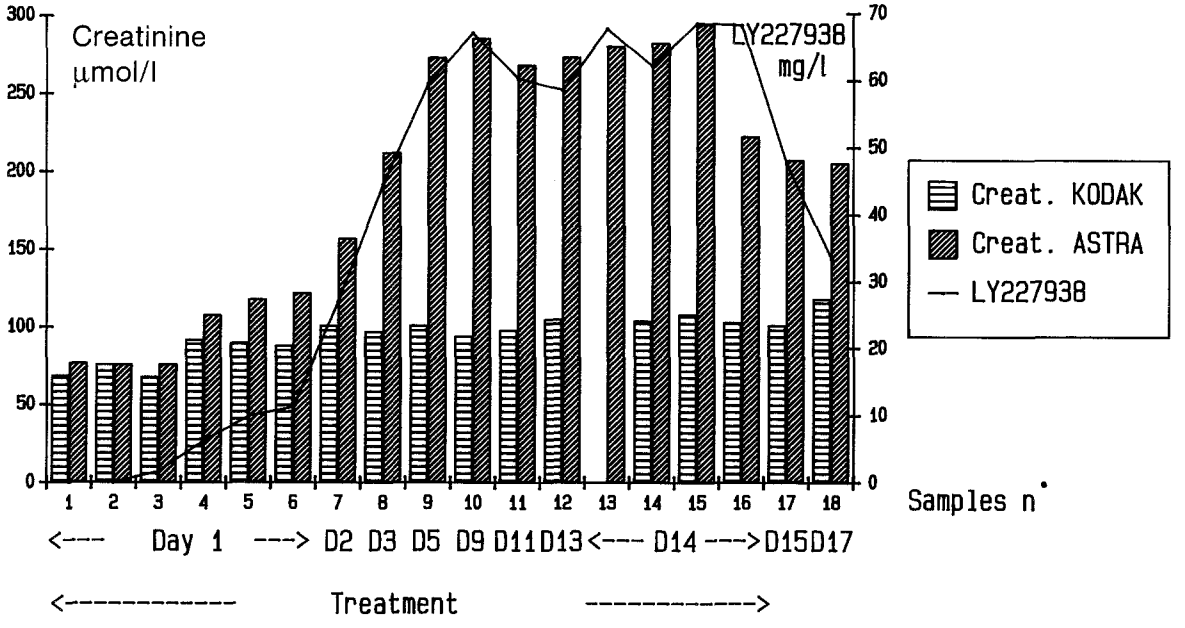

Fig. 1. In vivo interference of LY227938 with creatinine assay

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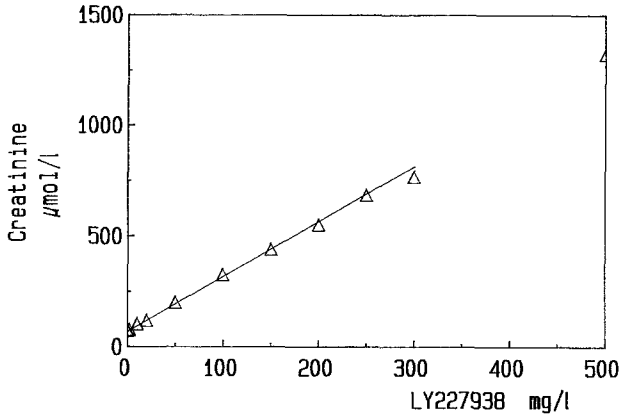

Fig. 2. In vitro interference of LY227938 with creatinine assay

The need for an alternative assay insensitive to this interference was obvious, even though renal toxicity could not be anticipated from toxicologic studies in animals. As can be seen in Fig. 1, the Single Slide Methodology (SSM) creatinine slides designed for use on the Kodak Ektachem 700 seem to be highly specific: the correlation coefficient between these two methods, as computed from 77 plasma samples drawn from patients who did not receive any known interfering substance, is 0.9888. Moreover, the interference pattern did not match the fluctuations in LY186641 determined by HPLC. The in vitro addition of the parent compound (LY186641) up to a final concentration of 300 mg/l to control plasma samples did not result in interference with the ASTRA method, nor did the addition of the hydroxy metabolite.

Kroll et al. [2] have documented the high reactivity of certain ketones toward picric acid and the resulting Jaffé reaction. Indeed, the addition of increasing quantities (up to 1,000 mg/l final concentration) of the keto metabolite (LY227938) to a pool of plasma assayed by both the Beckman and Kodak methods demonstrated an excellent linearity for this interference (Fig. 2). Although samples supplemented with 500 and 1,000 mg/l keto metabolite must be prediluted in 9‰ saline to fit within the ASTRA 8 analytical range, the obtained results remained on the regression line computed from 0 to 300 mg/l LY227938. The equation of this regression line is $y = 2.3692 \times + 77.54$ ($r = 0.9993$). These in vitro results were confirmed by the tight parallelism between interference height and LY227938 concentration observed in Fig. 1.

Conclusion

Major analytical interference with creatinemia determination may be considered to be a handicap for a new drug. However, in this phase I study the identification of the interfering compound and the subsequent proposal of an easy-to-operate, interference-free method overcame this handicap, paving the way for phase II clinical trials.

References

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