

MEDLINE Abstract

Comparative pharmacokinetics of submucosal vs. intravenous flumazenil (Romazicon) in an animal model.

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PURPOSE: This study was performed to determine the bioavailability and local tissue toxicological safety of flumazenil (Romazicon) when administered by oral submucosal (SM) as opposed to intravenous (i.v.) injection. **METHODS:** Six dogs each received SM flumazenil (0.2 mg), and their serum was collected at predetermined time intervals (0-2 h) and frozen (-70 degrees C). Seven days later, the dogs received an identical dose of i.v. flumazenil, and serum samples were again collected, as above. Comparative quantitation of flumazenil levels (i.v. vs. SM) was made using a sensitive HPLC assay (UV detection). Direct/local drug toxicity was visually scored by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. An oral pathologist examined slides processed from control and treatment tissues (hematoxylin and eosin staining) taken (punch biopsy) 1 week following SM injection to compare with direct clinical scores. **RESULTS:** Serum flumazenil levels reached a plateau (8.5 +/- 1.5 ng/mL, mean +/- SD) within 4 min of SM drug injection and declined thereafter to -2 ng/mL by 2 h. Bioavailability of SM flumazenil was 101 +/- 14%, based upon measuring the area under the serum concentration-time curves over 1.5 h (AUC 0-1.5 h, SM vs. i.v. drug). Thus, serum drug levels following SM drug administration were broadly comparable to those obtained during the elimination phase of corresponding i.v. drug delivery. Regarding drug tissue toxicity, no evidence of direct drug toxicity was observed by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. Following pathologic review, no difference was seen in the degree of inflammation between treatment and control tissue. **CONCLUSION:** At the quantity and concentration used, SM drug flumazenil administration appears to be both a safe and a viable alternative to bolus i.v. drug delivery and worthy of further investigation.

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