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Preparation and In Vivo Studies of a New Drug Delivery System

Nanoparticles of Alkylcyanoacrylate

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ABSTRACT

Polyhexylcyanoacrylate nanoparticles have been prepared with vincamine as the model drug. These particles had an average size of 200 nm and adsorbed approximately 43% of vincamine. The adsorption of vincamine to nanoparticles modified the distribution of vincamine in tissues. After iv injection the distribution volumes were increased in comparison with an aqueous solution of drug. In comparison with an aqueous solution of drug, the absolute bioavailability of vincamine was also increased after an oral administration of nanoparticles.

Index Entries: Polyhexyl cyanoacrylate, nanoparticles of; vincamine, adsorbed onto nanoparticles; pharmacokinetics and biopharmaceutics of nanoparticles; nanoparticles, of alkylcyanoacrylate; bioavailability, increases from nanoparticles

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INTRODUCTION

Recent studies have shown the importance of the concept of new carriers of drug in the pharmaceutical area. The purpose of the present study was to prepare nanoparticles of alkylcyanoacrylate and then study their fate in vivo.

Nanoparticles are polyalkylcyanoacrylate microspheres and have many important characteristics of a good drug delivery system. They can adsorb large amounts of drug and are also biodegradable. Their small size (50–500 nm) allows them entry into cells. Histologic studies concerning vinblastine adsorbed on nanoparticles have shown greater accumulation of drug in liver, lungs, and kidney than the free drug alone (*1*).

METHODS

The nanoparticles were prepared by the method of Couvreur (*2*). The model drug investigated was vincamine, an alkaloid of Vinca minor. The nanoparticles were prepared by polymerization of an alkylcyanoacrylate monomer. This alkylcyanoacrylate can be a methyl, ethyl, isobutyl, or hexylcyanoacrylate. The polymerization was induced by weak bases and the time of polymerization depended upon the type of monomer (from 1 h for methyl to 4 d for hexylcyanoacrylate). The alkylcyanoacrylate was added under stirring in an aqueous acidic medium in which is usually dissolved a polyose (Dextran 70)-like dispersant agent and surface active agent (TWEEN 20). After filtering (glass filter 5–15 μm) a milky suspension was obtained.

The pharmacokinetics and bioavailability of the suspensions of nanoparticles were studied in rabbits (n = 10 for each dose) by iv injection of 2 mg kg^{-1} of vincamine adsorbed onto nanoparticles and by oral administration of 10 mg kg^{-1} of vincamine adsorbed into nanoparticles by comparison with an aqueous solution of drug at the same dose.

RESULTS AND DISCUSSION

The maximal adsorption of this drug on the carrier was obtained with the monomer hexylcyanoacrylate and the average value of adsorption was 43%. The average size was approximately 200 nm. The formula of this suspension was as follows:

TABLE 1
Parameters of Bioavailability

Parameters	Aqueous solution	Nanoparticles suspension
Absolute bioavailability, F% (reference : IV sol)	22	36
Relative bioavailability, F% (reference: oral sol)	100	162

The absence of surface active agents in the formula demonstrated that as the alkyl chain of the acrylate increased, so did the surface active properties. It was with the longest alkyl chain (the most lipophilic) that the adsorption results were the best in relation to the lipophilic character of vincamine.

The results obtained were analyzed by a two-compartment model and showed a statistical increase of the half-life of drug elimination (79 min in solution vs 135 min in suspension) and in the distribution volumes (V_1/P = 1.7 L kg^{-1}, V_2/P = 2 L kg^{-1} for the solution vs V_1/P = 2.7 L kg^{-1}, V_2/P = 4.1 kg^{-1} for the nanoparticles). The body clearance was not statistically different for the solution and the suspension and was around 41 mL min^{-1} kg^{-1}. The important modification between the two forms is a different distribution of adsorbed vincamine on the nanoparticles. It was concluded that these modifications in distribution volumes were caused by intracellular transfer of the nanoparticles in the reticuloendothelial system, as suggested by previous histologic studies (*1*).

The results of the bioavailability studies are summarized in the following table.

Hexylcyanoacrylate	200 μL
Dextran 70	0.5 g
H_3PO_4 (*N*)	0.5 mL
H_2O *qs*	100 mL
Vincamine	200 mg

The absolute bioavailability was low for the aqueous solution and larger for the suspension. The relative bioavailability showed a dramatic increase of adsorption with the drug carrier. These results could be caused by the lipophilic character and the small size of the nanoparticles allowing a better transfer through the intestinal barrier and/or a protection of vincamine from digestive or hepatic degradation.

CONCLUSION

These results show that the hexylcyanoacrylate nanoparticles modify the drug distribution after iv administration, but can also increase the absorption process by oral route.

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