# Improved Lipid Lowering Activity of Bezafibrate Following Continuous Gastrointestinal Administration: Pharmacodynamic Rationale for Sustained Release Preparation of the Drug

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*Received November 11, 1998; accepted April 12, 1999*

***Purpose.*** To evaluate the role of different routes and modes of administration of bezafibrate (BZF) on its hypolipidemic activity. We hypothesize that the major sites of BZF action are located presystemically as in other "gastrointestinal (GI) drugs." Thus, continuous administration of the drug to the GI tract is expected to augment its efficacy and provides a rationale for an oral sustained release preparation of the drug.

***Methods.*** The hypothesis was investigated in three experimentally induced-hyperlipidemia rat models. Models A and B were based on cholesterol-enriched diets and Model C on induced acute hyperlipidemia by triton 225 mg/kg. The pharmacokinetics and the pharmacodynamics of the drug following various modes of administration were examined.

***Results.*** In all cases, continuous administration of the drug into the duodenum (IGI) at a dose of 30 mg/kg/day for 3 days (Models A and B) or over 18 hr (Model C) reduced significantly both total cholesterol and triglycerides levels and elevated HDL cholesterol levels in comparison to bolus oral administration of the same dose, as well as in comparison to equivalent intravenous infusion (Model C). Infusion of the drug directly into the portal vein produced an equivalent activity to IGI administration. The pharmacokinetic study showed 100% oral bioavailability, good colonic absorption properties and an indication for an enterohepatic cycle.

***Conclusions.*** The results confirm that BZF has a first pass hepatic pharmacodynamic effect. Administration of BZF in a slow release matrix tablet to the rats produced the same magnitude of effect as IGI administration, thus proving the pharmacodynamic rationale for this mode of administration for GI drugs.

**KEY WORDS:** bezafibrate; hyperlipidemia; pharmacodynamics; pharmacokinetics; sustained release.

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**ABBREVIATIONS:** BZF, bezafibrate; GI, gastrointestinal; PO, per-oral administration; IGI, continuous intraduodenal infusion; CHOL, total cholesterol; TG, triglycerides; HDL, high density cholesterol; AST, aspartate transaminase; IV, intravenous; SR, slow release; CA, colonic administration; IPI, intraportal vein infusion; AUC, area under the curve; MRT, mean residence time; MAT, mean absorption time; Vd, volume of distribution; BBB, blood brain barrier.

## INTRODUCTION

The aim of the present study was to evaluate the role of different routes and modes of bezafibrate (BZF) administration on its hypolipidemic activity. BZF is a fibric acid derivative that is used clinically to reduce blood lipoprotein levels, especially triglycerides (TG) (1). The mechanism by which BZF reduces TG concentration is not clear but is believed to be via increased catabolism of TG-rich lipoproteins due to stimulating effect of the drug on the activity of lipoprotein lipase, and to a lesser extent, hepatic triglyceride lipase. In addition, continuous treatment with BZF elevates high density lipoprotein (HDL) cholesterol levels.

We hypothesized that BZF is included in the category of "gastrointestinal drugs," that consists of medications that have sites of action (biophase) within the gastrointestinal (GI) tract, the portal vein or the liver. Although, drugs in this category are commonly used to treat local GI ailments, activation of presystemic biophases can also have systemic activity. It is expected that sustained administration of these drugs to the GI tract will improve the magnitude of pharmacologic response, while producing relatively low systemic drug concentrations. A practical technique for such drug targeting to presystemic biophases is an oral sustained release (SR) drug delivery system.

Our hypothesis was assessed in three experimentally induced-hyperlipidemia rat models into which the drug was administered in various modes and routes. Models A and B are based on cholesterol enriched diets. The experiments were conducted between the 3rd and 7th days after initiation of the special diets, when no tolerance to the state of hyperlipidemia occurs. We found that Sabra rats had higher susceptibility to cholesterol-rich diet than Lewis rats, a fact that enabled us to induce, in Model B, significant suppression of the HDL cholesterol fraction, that provided the means to assess the impact of the administration mode on the HDL/total cholesterol ratio, a clinically important parameter. In Model C, elevation of serum lipids was obtained by a non-specific lipase inhibitor Triton WR 1339 (2).

## METHODS

### Hypolipidemic Activity Evaluation

Rats were acquired from the animal-breeding unit of the Hebrew University Hadassah Medical School. They were stored in a light controlled room from 7:00 a.m. to 7 p.m.

*Model A*: Male Lewis rats weighing 200–230 g were given a cholesterol-rich diet containing 0.4% cholesterol and 0.2% cholic acid in ground standard chow *ad libitum*. The rats were fed the cholesterol-rich diet for 6 days. On the fourth day of the diet drug treatment was begun.

One group (PO) received peroral BZF 30 mg/kg/day as aqueous solution (b30), another group (IGI) received the same dose as a continuous infusion to the duodenum (throughout the entire period of the experiment) (2 cm below the portal sphincter) with an ALZET osmotic pump (Alza Corp., Palo Alto, CA) implanted at a dorsal position, under light ether anesthesia. Respective control groups received the vehicle (carbonate-bicarbonate buffer solution, pH = 10). Blood samples (0.7 ml) were taken from the tail under light ether anesthesia 3 days after BZF administration.



0724-8741/99/0700-1093$16.00/0 

*Model B*: Male Sabra rats weighing 200–230 g were given a lipid-rich diet (1.5% cholesterol, 0.5% cholic acid and 10% coconut oil in ground standard chow) *ad libitum* for 6 days, and on the fourth day BZF administration has started. The groups in this experiments were similar to those specified for model A except for an additional group (SR) that received once daily a slow release matrix tablet.

*Model C*: To examine the effect of BZF in an intense hyperlipidemic model, male Lewis rats weighing 280–350 g received triton WR-1339 (Tyloxapol$^R$-Sigma, Co. St. Louis MO) 225 mg/kg i.p. Following the triton injection, the rats received BZF by different modes and different doses, as follows: BZF (b) 30 mg/kg, perorally (PO) (b30), continuous duodenal infusion. (IGI), continuous infusion to the jugular vein (IV), continuous infusion to the portal vein (IPI), SR tablet (SR), and BZF 50 mg/kg (b50) was given either PO or IGI. The respective control groups received the vehicle solution either PO, IGI, IPI, or a placebo tablet. The continuous infusions (i.e., IGI, IV, IPI) were given over 18 hr, then, blood samples (0.7 ml) were obtained from the tail.

BZF serum concentration measurements were performed according to the method of Castoldi *et al.* (3). The minimal detectable BZF concentration in the serum was 50 ng/ml, the precision was 7%, relative standard deviation and accuracy was ±10%. BZF concentrations in tissues (i.e., liver, muscle, spleen, kidney) were determined similarly, except that an accurately weight tissue (300 mg) was homogenized with I ml of normal saline solution that contained 50 µl of the internal standard solution (0.01% clofibric acid) and 30 µl of hydrochloric acid 1 N. The fibrate derivatives were extracted with 5 ml diethylether that was subsequently evaporated to dryness.

Total cholesterol (CHOL), triglycerides (TG), HDL cholesterol (HDL) and aspartate transaminase (AST) (for liver function assessment) were determined by the "Kodak Ektachem, Clinical Chemistry Products" dry method chemistry autoanalyzer (4).

Small dimension SR tablets were developed to allow oral administration in rats. Each tablet contained BZF in a dose of 30 mg/kg. The drug was mixed with hydroxypropyl methylcellulose Methocel™ K4M and directly compressed in a 5 mm punch under 3 ton pressure for 0.5 min. The tablets released the drug at a constant rate over 10 hr in phosphate buffer (pH = 6.8), according to the USP dissolution test specifications. To administer the SR tablets to the rats a novel technique was developed (5).

### Pharmacokinetic Evaluation

Male Lewis rats, weighing 280–350 g, recieved BZF 30 mg/kg as an IV bolus, PO, IGI for 12 hr or to the colon (CA). Blood samples (100 µl, up to 10 hr, and 200 µl thereafter) were taken from the jugular vein at specified time points.

In order to assess the tissue distribution of BZF Lewis rats were sacrificed 7 hr after administration of BZF 30 mg/kg PO and IGI, and BZF concentrations were determined in serum, liver, kidney, spleen and muscle.

To examine the bile secretion of BZF the drug (10 mg/kg) was administered by infusion over 15 min to the jugular or to the portal vein. Then, the rats were sacrificed, and the serum, liver and bile fluids were collected and assayed for BZF.

Binding of BZF to rat and to human serum proteins was determined by equilibrium dialysis at 37°C against an equal volume of 0.13 M sodium and potassium phosphate buffer solution pH 7.4.

### Data Analysis

The results of the studies are presented as the difference between each parameter in the treatment group and its respective control group normalized to the control value. This approach was adopted to overcome the effect of the delivery system and the difference between lots of rats on lipid levels. Results are reported as mean ± SD.

The statistical assessment of the data was made by Kruskal-Wallis test followed by the Mann-Whitney test where appropriate. Noncompartmental pharmacokinetic data analysis was performed using the WinNonlin computer program.

## RESULTS

### Pharmacodynamic Evaluation

*Model A*: The effect of BZF given by various routes of administrations on the serum lipid concentrations of Lewis rats with experimentally induced hyperlipidemia are shown in Table I. The reduction in cholesterol (CHOL) level was 25% with IGI administration, whereas there was no effect with the same dose of BZF given PO. A more pronounced effect was observed on triglyceride (TG) levels that were reduced by 61% following IGI infusion in comparison to a much more modest impact following PO dosing regimen (17%). The HDL/CHOL ratio was elevated with IGI administration by 30% in comparison to the control parallel group, while peroral administration of the same BZF dose had only a relatively small impact on this parameter.

**Table I.** The Effect of BZF 30 mg/kg/day Following PO and IGI Infusion for 3 Days on Cholesterol (CHOL) and Triglyceride (TG), the HDL Cholesterol (HDL) and the Ratio Between HDL and Total Cholesterol (CHOL) HDL/CHOL, in Male Lewis Rats Fed CHOL-Rich Diet (Model A)

| | CHOL (mg%) CONT | BZF | % Δ | TG (mg%) CONT | BZF | % Δ |
|---|---|---|---|---|---|---|
| PO | 91 ± 5 | 88 ± 5 | −3 | 114 ± 13 | 95 ± 10 | −17 |
| IGI | 84 ± 17 | 62 ± 9* | −25 | 127 ± 14 | 49 ± 9** | −61 |
| | HDL (mg%) CONT | BZF | % Δ | HDL/ CHOL CONT | BZF | % Δ |
| PO | 47 ± 9 | 44 ± 2 | −6 | 0.52 ± 0.04 | 0.61 ± 0.02 | 17 |
| IGI | 40 ± 12 | 38 ± 4 | −5 | 0.53 ± 0.1 | 0.69 ± 0.07* | 30 |

*Note:* Statistically significant difference between drug treated group and its corresponding control group * ($p < 0.01$); ** ($p < 0.002$). Results are reported as mean ± SD, ($n = 10$). The Δ represent the difference (in percent) between the drug treated and the corresponding control group.

*Model B*: The effects of various routes of BZF administrations on serum lipid concentrations in Sabra rats with experimentally induced hyperlipidemia are shown in Table II. It was found that serum lipid levels of both CHOL and TG showed a greater reduction by IGI and SR administration modes as compared to PO. The same trend was also found in the magnitude of TG response. The HDL serum levels were elevated by both IGI and SR administration by about 50% and 100% respectively, while the effect achieved by PO administration was negligible. Subsequently, the HDL/CHOL ratio was markedly increased following both IGI and SR administration (143% and 511%, respectively) in comparison to the parallel control groups. The same BZF dose given PO resulted in a significantly smaller effect on the HDL/CHOL ratio (65%).

*Model C*: The effects of BZF given via various routes of administration on the serum lipid concentrations of Lewis rats with acute experimentally-induced hyperlipidemia are shown in Table III. BZF at a dose of 30 mg/kg reduced both CHOL and TG levels more pronouncedly when given by continuous modes of administration, either IGI or SR, as compared to PO administration. The reduction in serum CHOL following 50 mg/kg BZF administration IGI was 39% in contrast to a very limited effect following PO administration. Similar results were found for the effect on TG levels. The reduction of serum lipids following IV continuous infusion of 30 mg/kg BZF over 18 hr was negligible. Higher BZF dose of (50 mg/kg) given by continuous IV infusion produced a reduction of 25% in CHOL serum levels and 12% in the TG.

Portal infusion (IPI) of BZF 30 mg/kg provided the most dramatic effects on the serum lipids; CHOL levels were reduced by 52% and TG by 60%.

BZF serum concentrations 18 hr after initiation of drug administration (30 mg/kg) in model C were found to be 14 ± 5, 56 ± 16, 48 ± 13, 22 ± 8 and 14 ± 8 μg/ml for PO, IV, IGI, IPI and SR modes of administrations, respectively, and 32 ± 18, 92 ± 11 and 57 ± 11 μg/ml for a dose of 50 mg/kg given by PO, IV and IGI respectively. It can be seen that BZF serum concentration in most groups were in the range of 14–57 μg/ml, and the only differing group was the IV infusion of the 50 mg/kg dose that was significantly higher. It is important to note that this high BZF concentration in the systemic circulation was not associated with significant impact on serum lipids as mentioned above.

**Table II.** The Effect of BZF 30 mg/kg/day Following PO, IGI Infusion and by Slow-Release Tablet (SR) for 3 Days on Cholesterol (CHOL) and Triglyceride (TG), the HDL Cholesterol (HDL) and the Ratio Between HDL and Total Cholesterol (CHOL) HDL/CHOL, in Male Sabra Rats Fed CHOL-Rich Diet (Model B)

| | CHOL (mg%) CONT | BZF | % Δ | Tg(mg%) CONT | BZF | % Δ |
|---|---|---|---|---|---|---|
| PO | 210 ± 13 | 151 ± 44* | −28 | 250 ± 21 | 170 ± 51* | −32 |
| IGI | 248 ± 30 | 140 ± 23** | −44 | 137 ± 20 | 81 ± 15* | −41 |
| SR | 316 ± 13 | 113 ± 30** | −64 | 225 ± 23 | 102 ± 34** | −55 |
| | HDL (mg%) CONT | BZF | % Δ | HDL/ CHOL CONT | BZF | % Δ |
| PO | 36 ± 4 | 39 ± 11 | 8 | 0.17 ± 0.02 | 0.28 ± 0.03* | 65 |
| IGI | 30 ± 5 | 45 ± 9* | 50 | 0.14 ± 0.04 | 0.34 ± 0.02** | 143 |
| SR | 23 ± 2 | 46 ± 13** | 100 | 0.09 ± 0.01 | 0.55 ± 0.08** | 511 |

*Note:* Statistically significant difference between drug treated group and its corresponding control group * ($p < 0.01$); ** ($p < 0.002$). Results are reported as mean ± SD, ($n = 10$).

**Table III.** The Cholesterol (CHOL) and Triglyceride (TG) Lowering Effect of Bezafibrate 30 mg/kg (b30) or 50 mg/kg (b50) Following Bolus PO Administration or Continuous Infusion of the Drug Over 18 hr into Either the Duodenum (IGI), the Jugular Vein (IV) or the Portal Vein (IPI), or Following Administration of Slow Release Bezafibrate Tablets (SR), to Male Lewis Rats with Hyperlipidemia Induced by an i.p. Injection of Triton 225 mg/kg (Model C)

| | CHOL (mg%) CONT | BZF | % Δ | TG (mg%) CONT | BZF | % Δ |
|---|---|---|---|---|---|---|
| PO b30 | 219 ± 17 | 248 ± 28 | 13 | 390 ± 52 | 353 ± 29 | −9 |
| IGI b30 | 232 ± 26 | 183 ± 19* | −21 | 461 ± 56 | 327 ± 44* | −29 |
| SR b30 | 216 ± 13 | 176 ± 15* | −19 | 448 ± 54 | 227 ± 65** | −49 |
| PO b50 | 219 ± 17 | 190 ± 46 | −13 | 390 ± 52 | 367 ± 72 | −6 |
| IGI b50 | 232 ± 26 | 141 ± 24** | −39 | 461 ± 56 | 222 ± 52** | −52 |
| IV b30 | 211 ± 26 | 203 ± 9 | − 4 | 434 ± 66 | 391 ± 10 | −10 |
| IPI b30 | 232 ± 38 | 111 ± 14** | −52 | 446 ± 48 | 178 ± 31** | −60 |
| IV b50 | 211 ± 26 | 159 ± 20* | −25 | 434 ± 66 | 380 ± 54 | −12 |

*Note:* Statistically significant difference between drug treated group and its corresponding control group * ($p<0.05$); ** ($p< 0.005$). Results are reported as mean ± SD, ($n = 10$).

## Pharmacokinetic Study

The pharmacokinetic parameters calculated according to non-compartment analysis are shown in Table IV. The similarity in the AUC values revealed complete absorption of BZF via PO and SR administration, the availability in the CA administration was 44%. The $t_{1/2}\beta$ in all routes ranged between 6 to 10 hours. Unbound BZF fraction was 9.7 ± 0.9% in rat serum

**Table IV.** Pharmacokinetic Parameters of Bexafibrate Calculated by the Noncompartmental Method Following Various Modes of Administration of Bezafibrate 30 mg/kg Given to Male Lewis Rats[a]

| Parameter | IV | PO | CA | IGI |
|---|---|---|---|---|
| AUC (hr μg/ml) | 602 ± 259 | 789 ± 157 | 267 ± 134[b] | 697 ± 86 |
| $t_{1/2}$ β (hr) | 8.54 ± 4.2 | 10.15 ± 2.6 | 6.6 ± 2 | 8.8 ± 2 |
| MRT (hr) | 9.3 ± 1.8 | 10.9 ± 1.7 | 11.2 ± 3.1 | 12.8 ± 2.9* |
| Tmax (hr) | | 4 ± 2.17 | 2.1 ± 1.2 | 6 ± 1 |
| Cmax (hr) | | 56.3 ± 12 | 33 ± 23 | 45.5 ± 6.8 |
| CL/F (ml/hr/kg) | 48.5 ± 19.8 | 41.2 ± 9.3 | 113.5 ± 56.7 | 43.5 ± 5.4 |
| MAT (hr) | | 1.7 | 1.9 | 3.5 |

[a] The drug was given as a bolus dose to the jugular vein (IV), perorally (PO), and into the colon (CA), or by a continuous infusion (over 12 hr) to the duodenum (IGI) ($n = 5$);

[b] AUC values following CA administration were significantly different from the other modes of administration ($p < 0.05$); * MRT following IGI is significantly different from the MRT following IV, PO, and CA administration ($p < 0.05$). Result are reported as mean ± SD.

[c] Calculated with the mean data.

and 7.7 ± 0.9% in human serum. Steady state volume of BZF distribution calculated from IV data was 526 ± 58 ml/kg.

Liver and kidney BZF concentrations 7 hr after administration of BZF 30 mg/kg were found to be significantly higher than serum BZF levels.

BZF concentrations following administration of the drug (10 mg/kg) via either jugular and portal vein infusion for 15 min were found to be 36.7 ± 12.5 μg/ml and 30.3 ± 2.5 μg/ml in the serum and 65.9 ± 23 μg/ml and 46 ± 17 μg/ml in the liver, respectively. The rate of biliary elimination of unchanged BZF was found to be 0.713 ± 0.25 μg/min for IV and 0.433 ± 0.18 μg/min for IPI.

AST levels at the end of all the experimental models were found to be within the normal range.

## DISCUSSION

The results of this investigation support our hypothesis that BZF has presystemic sites of action and thus can be regarded as a "GI drug." This conclusion is based on results indicating that equivalent doses of the drug produced significantly elevated hypolipidic activity when given at a slow rate directly to the GI tract compared to a PO bolus and even to a slow IV infusion. Specifically, in Model A, IGI administration of BZF significantly reduced (over 3 fold) both CHOL and TG levels and elevated the HDL/CHOL ratio in comparison to PO administration of the same dose. Similar results were also found in Model B.

The super-enriched diet protocol (Model B) enabled us to assess the effect of mode of administration on HDL levels, a parameter that is an important clinical goal in antihyperlipidemic therapy. The data proved that IGI administration of BZF elevated serum HDL levels by 49% while the PO mode did not affect this parameter. Consequently, the HDL/CHOL ratio was also notably elevated (over 140%) by the IGI infusion.

While in Models A and B hypercholesteremia was produced in healthy rats with normal enzyme function, in Model C acute hyperlipidemia was produced by inhibition of the lipoprotein lipase enzymes that are responsible for the removal of lipid particles from the blood (2). The administration of triton causes a transient elevation of lipid levels that reaches a peak about 18 hr after triton administration and disappears several days later (6). This experimental model has been used before for screening the activity of antilipidemic agents, including BZF (2). In this model the differences between the hypolipidemic effects subsequent to PO and IGI modes of administration followed the same trend found for the CHOL rich diet-induced hyperlipidemic models.

A major conclusion derived from this investigation is the lack of direct correlation between the systemic drug concentration and magnitude of effect. This conclusion is further demonstrated in Model C. It was found that although the rate of drug administration by the IV infusion mode was equal to that of the IGI administration, the magnitude of lipid lowering effect was significantly less ($P < 0.05$). The magnitude of this pharmacologic effect was in contrast to the elevated serum concentration detected following IV infusion in comparison to IGI at the experimental endpoint, 18 hr post triton administration.

In our view, this lack of correlation between the blood concentration and magnitude of effect, occurs in those cases where the systemic blood drug concentrations are not in a rapid equilibrium with the site(s) of action. This disequilibrium may arise from biological barriers, acute up-or down-regulation of the receptor/effector units or, as in this case, due to targeting of the drug specifically to the site(s) of action. In fact, for GI drugs, continuous administration to the GI tract serves as a "targeting system" since the drug concentrations "seen" by the presystemic sites of action before the drug molecules are introduced to the systemic circulation are considerably larger than following dilution in the entire volume of distribution. Thus, in accord with the concept of "targeting," the systemic concentration may be minimal at the time the drug is delivered directly to the biophase.

Since in addition to the liver, the intestine has also been identified as a source of cholesterol synthesis and metabolism (7), the augmented effect of the intestinal administration could be due to action on either the intestine wall (8), the liver or both. In order to identify the major sites of BZF activity the drug was infused directly into the portal vein (IPI administration). Since the magnitude of effect following IPI was similar to that of IGI it can be concluded that the intestine has a minor role in reducing the lipid levels, and the major site of action is in the liver. This is specifically true for Model C and should be further validated in the other experimental models. The results indicate that BZF has "a hepatic first pass dynamic response" (in contrast to the known phenomenon of "first pass elimination").

There are certain characteristic pharmacokinetic properties that can improve the efficacy of the IGI approach for GI drugs.

### *Rate of GI Absorption*

In the case of a drug that is rapidly absorbed, a slow IGI administration would yield superior effects than PO administration of the drug. For BZF, the rate of absorption was found to be relatively slow with a mean absorption time (MAT) of 1.7 hr. According to this rationale, further reduction of the rate of BZF absorption, by means of slow sustained release dosage form, is expected to improve activity.

### *Enterohepatic Cycle*

We discovered that BZF undergoes a reabsorption process according to the enterohepatic cycle. This finding is concluded on the basis of the following findings: a) BZF is secreted unchanged via the bile duct; and b) the drug has good GI absorption properties and it can be absorbed both from the small intestine as well as from colon (discussed below). This enterohepatic cycle enhances the availability of the drug to the presystemic sites of action (even following direct administration into the systemic blood circulation), and is an important feature in the case of a drug like BZF with a hepatic first pass dynamic response.

### *Rate of Elimination*

GI drugs with very short biological half-life are the best candidates for the IGI approach. This mode of administration will control the rate of drug exposure to the presystemic sites of action while the systemic concentration will be very low. Thus, it will minimize concentration-dependent adverse effects. However, BZF is eliminated relatively slowly (half-life about 8.5 hr), thus relatively high systemic BZF concentrations can

be found following repetitive administrations. Nonetheless, as discussed above, there was no correlation between the systemic drug concentration and magnitude of effect.

*Volume of Distribution (Vd)*

The IGI approach is more suitable for a GI drug with large Vd because it yields relatively low systemic concentrations of the drug in comparison to the presystemic concentrations. It was found that BZF has a Vd of about 500 ml/kg that is large enough to cause pronounced differences between the pre- and post distribution concentrations.

*Accumulation in Target Organs*

We have found that BZF tends to accumulate in specific organs such as the kidneys and the liver. No statistically significant difference was found between the drug concentration in the liver following IV and IPI administration. Therefore, the difference in magnitude of effect may indicate that the sites of action are located in the periportal zone rather than symmetrically spread in the liver.

*Colonic Absorption*

Once the hypothesis of improved efficacy following IGI administration has been confirmed, the colonic absorption properties of the drug must be assessed. Good colonic absorption indicates that the continuous administration of the drug can be maintained along the whole GI tract and the drug can be formulated as a SR tablet. As expected from a lipophilic drug with low MW such as BZF, the drug proved to be absorbed following intra-colonic administration.

*Degree of Serum Protein Binding*

A possible explanation for the difference in the magnitude of pharmacologic effect between the intravenous and IGI modes of BZF administration could evolve from the large degree of BZF binding to serum proteins which was found to be over 90%. The time elapsed between the appearance of a drug molecule that crosses the intestine wall until it reaches the liver is less than a second. In theory, if the binding process of the drug to the serum proteins does not reach its maximal capacity within the first passage through the portal vein, the unbound fraction (and thereby, unbound concentration) of the drug delivered to the presystemic sites of action would be much greater than after an equilibrium of the binding process has been reached. Although, many reservations can be raised against this explanation, it is in accord with the results typically found in another experimental procedure, the single intra-carotid injection for the measurement of blood brain barrier (BBB) permeability. The similarity between the two systems is due to the fact that the BBB permeability is measured following a very short transit time of the drug, the single passage from the injection site at the lower neck area to the brain. The outcomes there have demonstrated a lack of correlation between drug uptake by the brain and the unbound fraction of the drug measured in vitro (9,10). There is no further data to challenge this theory because typical binding experiments did not concentrate on the initial milliseconds of the process but rather on steady state conditions.

The practical utilization of the above results is as a pharmacodynamic rationale for developing an oral sustained release dosage form that will release its contents in a prolonged slow release manner into the GI tract. Contrary to pharmacokinetic rationale, which is based on achieving certain systemic drug concentrations in order to assure activity, the pharmacodynamic rationale is based directly upon the magnitude of effect. This approach is especially required in those pharmacologic effects with no direct correlation between drug concentration and magnitude of response. We have examined this pharmacodynamic rationale by comparing the antihyperlipidemic effect of BZF delivered continuously from a slow release dosage form to the activity of the drug given by the other modes of administrations. Our results indicate that the magnitude of lipid lowering activity and elevation of HDL levels following SR-BZF is similar or better to that achieved following IGI administration. Thus, both modes of prolonged administration (that provide constant dripping of the drug along the GI tract) optimize BZF activity. The same trend was observed in a recent investigation preformed with niacin, another hypolipidemic agent (5).

## ACKNOWLEDGMENTS

Dr. A. Hoffman and Prof. M. Friedman are affiliated with the David R. Bloom Center for Pharmacy.

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