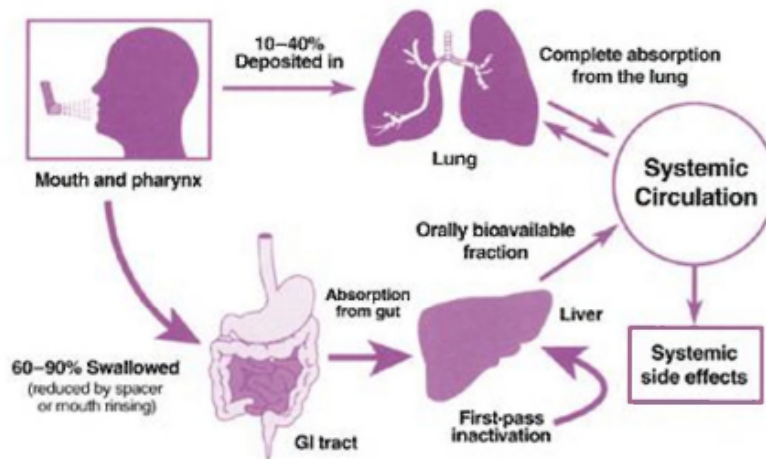


Inhaled Steroids in Asthma

Optimizing Effects in the Airways



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II. Soft Drugs

Soft drugs represent a possible solution, as they may eliminate the problems caused by the possibility of formation of various metabolites and they can minimize systemic side effects. Soft drug design approaches represent new approaches aimed to design safer drugs with an increased therapeutic index by integrating metabolism considerations into the drug design process (6, 7). The soft drug concept was introduced in 1976 (8) and reiterated on a number of occasions in 1980–81 (9–14). Soft drugs are new therapeutic agents that undergo predictable metabolism to inactive metabolites after exerting their therapeutic effect. They are designed by building into the molecule, in addition to the activity, the most desired way in which the molecule is to be deactivated and detoxified subsequent to exerting its biological effects. The desired activity is generally local, and the soft drug is applied or administered at or near the site of action. Therefore, in most cases, they produce pharmacological activity locally, but their distribution away from the site results in a prompt metabolic deactivation that prevents any kind of undesired pharmacological activity or toxicity.

Inclusion of a metabolically sensitive site into the drug molecule makes possible the design and the prediction of the major metabolic pathway and avoids the formation of undesired toxic, active, or high-energy intermediates. Hence, in soft drug design, the goal is not to avoid metabolism, but rather to control and direct it. If possible, inactivation should take place as the result of a single, low-energy, high-capacity step that yields inactive species subject to facile elimination. Most critical metabolic pathways are mediated by oxygenases that exhibit not only interspecies but also interindividual variability and are subject to inhibition and induction (15). In different individuals, half-lives of foreign compounds may vary as much as 10- to 50-fold (15). Furthermore, the rates of hepatic monooxygenase reactions are at least two orders of magnitude lower than the slowest of the other enzymatic reactions (16). Therefore, it is usually desirable to avoid oxidative pathways and slow, easily saturable oxidases and to design soft drugs that are inactivated by hydrolytic enzymes. Metabolism can be more reliably carried out by ubiquitous esterases, because they are widely distributed, nonspecific, and much less susceptible to saturation and inhibition. Because diseases can alter the organs responsible for the metabolism of bloodborne substances, it is better not to rely on metabolism or clearance by organs such as liver or kidney since blood flow and enzyme activity in these organs can be seriously impaired, especially in critically ill patients.

Carboxylic ester hydrolases (EC 3.1.1) efficiently catalyze the hydrolysis of a variety of ester-containing chemicals to the respective free acids. They exhibit broad and overlapping substrate specificity toward esters and amides, and the same substrate is often hydrolyzed by more than one enzyme. Consequently, their classification is difficult and still is in a somewhat confused state, despite the important roles that carboxylesterase (EC 3.1.1.1) and/or other carboxylic ester hydrolases, such as arylesterase (EC 3.1.1.2) and cholinesterase (EC 3.1.1.8), play in the metabolism of many xenobiotics (17–23). Humans have been shown to express carboxylesterase in the liver, plasma, small intestine, brain, stomach, colon, macrophage, and monocytes (23). It should be mentioned that esterase activity varies quite strongly between species (17–23). For

example, the stability of aliphatic esters frequently employed in prodrug and soft drug designs usually increases in the rat<rabbit<dog<human order (24, 25), but there might be considerable variability. Nevertheless, we have recently succeeded in developing a quantitative structure-metabolism relationship (QSMR) model that accounts for 80% of the variability in the log half-lives of 67 noncongener carboxylic esters for *in vitro* human blood data and that should be useful in estimating approximate rates of hydrolysis even ahead of synthesis (26, 27).

The general principles of soft drug design and their practical applications have been reviewed in the literature (6, 7, 28–30). A number of already marketed drugs, such as esmolol (Brevibloc[®]), an ultra-short-acting β -blocker, remifentanyl (Ultiva[®]), a unique ultra-short-acting opioid analgesic, or loteprednol etabonate (Lotemax[®], Alrex[®]), a soft corticosteroid, resulted from the successful application of such design principles (7). Within the corticosteroid field, various attempts have been made to separate local and systemic effects by integrating moieties susceptible to facile, extrahepatic metabolism into the corticosteroid structure (31–37). Here, we will concentrate mainly on an attempt that at present can be considered as the most successful one along these lines. It is a classic, inactive metabolite-based soft drug approach that started from a true inactive metabolite of prednisolone (9) and ultimately yielded loteprednol etabonate (7) (Fig. 2).

At this point it should be mentioned that some other steroid drugs, such as fluticasone propionate, tipredane, or butixocort 21-propionate, have been erroneously called soft drugs on different occasions (4, 38). Contrary to the previously mentioned soft drug design principles, these structures are metabolized primarily in the liver by oxidative processes and not by extrahepatic hydrolysis. Thiol ester corticosteroid structures have been shown to be metabolized primarily in the liver by oxidative processes, rather than by hydrolysis in the plasma (39). Fluticasone propionate (FP) itself was found to have a terminal half-life of 7.7–8.3 hours in 12 healthy male subjects after inhaled administration of 500, 1000, and 2000 μ g of drug using a metered-dose inhaler. In these subjects it produced dose-related cortisol suppression, the highest administered dose of FP resulted in cortisol concentrations that were lower than the limit of detection (40). The slow elimination of FP led to accumulation during repeated dosing. This accumulation may explain the marked decrease in plasma cortisol seen during treatment with fluticasone propionate within the clinical dose range (41).

There also is some misconception regarding soft drugs, particularly soft steroids. Often, the soft nature is associated with fast hydrolytic degradation, but this is not necessarily so. Too fast hydrolysis could result in very weak activity. The desired increase of the therapeutic index can be achieved only if the drug is sufficiently stable to reach the receptor site and the target organ and to produce its desired effect, but the free, non-protein-bound drug undergoes facile hydrolysis to avoid unwanted, systemic side effects. In order to successfully separate the desired local activity from systemic toxicity, an adequate balance between intrinsic activity, solubility/lipophilicity, tissue distribution, protein binding, and rate of metabolic deactivation has to be achieved, particularly for long-term activity. In the case of slow, sustained release to the general circulatory system from the delivery site, even a relatively slow hydrolysis could result in a very low, almost steady-state systemic concentration.