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REVIEW

Absorption of Drugs from the Bladder and Intravesical Chemotherapy

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It is generally not appreciated that the urinary bladder is not only a reservoir but also on organ that is able to absorb various substances through its mucosal lining.

This is not without interest considering that many drugs are occasionally employed for intravesical instillation. In particular, thio-tepa and other anticancer drugs are frequently employed topically for non-invasive papillary bladder tumours with a relatively high rate of successful results. Absorption of thio-tepa can however be followed by severe or even lethal myelotoxicity. Because of this epodyl has been recommended as a substitute for thio-tepa due to its higher molecular weight. The laws governing absorption from the bladder are however poorly understood.

Ancient and recent studies on the permeability of the urinary bladder in mammals have shown that water, electrolytes, dextrose and other organic and inorganic molecules are absorbed through the bladder wall (1, 3, 14, 15, 16). Detailed investigations by Fellows et al. (8) have demonstrated that the permeability of the bladder to water and solutes is greater than that of the skin (by a factor of about a thousand with regard to water) but similar to that of gastric mucosa and other biological membranes. In spite of some conflicting results, it seems that the epithelium of the bladder usually acts as a passive barrier. Transport of water, sodium and other solutes, therefore, is affected primarily by the laws of diffusion along concentration or osmotic gradients and unaffected by metabolic inhibition. No convincing evidence has been put forward in favour of the hypothesis of active transport of solutes across the epithelium. Active transport was postulated only under particular experimental conditions, such as the use of stripped vesical epithelium in vitro.

No satisfactory explanation has been presented to account for the variable rate of permeability to various drugs, although absorption can be modified by factors such as pH of the solution, molecular weight of the substances concerned etc. The role of molecular weight is not yet clear. Strohmenger (22), - for example, demonstrated that the human bladder can absorb the large molecule of p-aminohippurate but is impermeable to calcium and phosphorus. Permeability to Na^{22} is increased during distension (11) or when the bladder contains hypertonic solutions (23), but these aspects need to be clarified by more detailed investigations using substances other than electrolytes. For a comprehensive review of the pertinent literature the reader is referred to the reports by Englund (6), Fellows and Turnbull (9), Mentasti and Gagliardi (17) and Pavone-Macaluso et al. (20).

The human bladder shows a permeability to water and sodium similar to that of the other mammalian species, despite some minor differences. This is also true for the rabbit bladder (23) which can therefore be employed for experiments on the absorption of drugs used in humans.

Absorption across the bladder wall is altered in the absence of an intact epithelial layer. Transfer across the vesical mucosa is greatly enhanced if the bladder epithelium is damaged following contact with chemicals, such as dimethylsulphoxide (2) and cyclophosphamide. Instillations of cytotoxic drugs repeated at frequent intervals may therefore be followed by significant absorption even if the first instillation only gives rise to minimal diffusion. Permeability coefficients of human bladder epi-

thelium to tritiated water (THO) and labelled sodium are markedly increased in the presence of urinary infection and after previous radiotherapy. Well differentiated tumours enhance the permeability because of the increase in epithelial surface area. Absorption however is highest if anaplastic carcinoma is present (7). This latter finding is consistent with the observation that tight intercellular junctions are lacking in undifferentiated tumours, so that the intercellular spaces communicate freely with the bladder lumen.

Practical implications of studies on bladder permeability are mainly related to the use of intravesical instillations of thio-tepa or other anticancer drugs, either as a treatment of multiple papillomas and diffuse papillomatosis or as a measure for achieving a decrease of recurrence rate after successful transurethral removal of papillary bladder tumours. Severe myelotoxicity and even death from generalised sepsis may follow intravesical treatment with thiotepa (4, 24). Experimental data on the absorption of thiotepa from the bladder wall are scarce. Georgacopulo et al. (10) demonstrated that thiotepa labelled with S^{35} is absorbed from the dog's bladder and can be found in the muscular layer and in the hypogastric lymph nodes. Cole et al. (5) observed that thiotepa can be detected in peripheral blood following intravesical instillation in dogs. Absorption was greater if the urine was alkaline. Lunglmayr and Czech (12) demonstrated that absorption of thiotepa from the human bladder can reach 38 % of the administered dose in the presence of large papillary tumours, 58 % in cases of diffuse papillomatosis, 47 % in cases of cystitis and as much as 91 % following transurethral surgery. Absorption of thio-tepa can be enhanced if a hyperthermic solution is employed, as suggested by Lunglmayr et al. (13) or if vesicoureteric reflux is present (18).

Other drugs have been successfully used by intravesical instillation, although the overall experience is still limited. Epodyl (21), adriamycin, daunomycin, VM26, Peptichemio and other drugs were found capable of inducing regression of already established tumours or of reducing recurrence rate (19). No myelotoxicity was ever observed after instillations of drugs other than thiotepa, but almost nothing is known about their absorption.

In conclusion, it seems that our present knowledge of the absorption of drugs from the bladder is incomplete. Further studies are necessary considering the importance of the practical implications, especially in the field of topical chemotherapy.

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