

DERMATOLOGIC USES OF UREA

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It sometimes happens in the enthusiastic search for new therapeutic agents that some old stand-by has been overlooked whose luster has worn off, but which nonetheless may have some useful application in moments when the miracle drugs falter. In the world of topical therapy, urea is such a drug. Its dermatologic benefits lie in its bacteriostatic and proteolytic properties. By removing bacteria and non-viable tissue detritus, it has the double role of bacteriostasis and chemical debridement.

Present knowledge of urea may be summarized as follows:

1. Bacteriostatic action. Symmers and Kirk (1) long ago found 10 % solutions to be inhibitory against certain organisms. In this concentration, I found it to be a "wide-spectrum" antibacterial agent in vitro against a variety of organisms recovered from many different types of cutaneous lesions, viz; coagulase positive micrococci, beta hemolytic streptococci, miscellaneous aerobic streptococci, gram negative rods (*Escherichia*, *Pseudomonas* and *Proteus*), and all the resident species of the skin. Bactericidal effects are not obtainable with any constancy against the gamut of organisms encountered in dermatologic work except with concentrations exceeding 40 %. Certainly by modern standards exemplified by the antibiotics which are often active in less than one part per million, the antiseptic action of urea is feeble and unimpressive; however, it is entirely practical to use urea topically in concentrations of 40 % and more, owing to its lack of toxicity, at which strengths its antibacterial effects are something of a match for the antibiotics, with the further advantage that all the common organisms are susceptible and the possibility of resistant strains need not be seriously considered. Let it be said at once that the topical antibiotics do not stand in the slightest danger of being displaced by urea.

In a 10 % concentration, I found urea to be fungistatic for the common pathogens, the ringworm organisms and the deep fungi. With the possible exception of cutaneous moniliasis, I see no possible clinical application of the antifungal powers of urea.

2. Proteolytic action. Spiro (2) was the first to show the dissolution of proteins by strong solutions of urea, a fact later rediscovered by Ramsden (3) who also observed that it prevents the coagulation of proteins by heat. Fibrins, globulins and albumins swell up and dissolve in strong urea solutions. Crystalline pepsin is 10 times more soluble in urea solutions than in water (4). If practical proof of the lytic effect of urea is wanted, it is to be found in Ramsden's demonstration that a dead frog immersed in a saturated solution of urea becomes translucent and falls to pieces in a few hours. I enlarged upon this experiment in the following way: guinea pigs were infected with *T. mentagrophytes* which produces within 14 days an intense inflammatory dermatitis with marked

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crusting and scaling. Full thickness pieces of this dermatitic skin, about 2 inches square, were immersed overnight in a series of aqueous urea solutions ranging from 10 % to 70 % and the effects compared to immersion in water. Within the ranges of 40—70 %, the skin became swollen, soft and somewhat jelly like, with a slimy feel. The voluminous gelatinous crust simply fell apart when rubbed lightly with the finger. This effect was less marked with the 30 % solution and was not appreciable in the 20 % concentration and below. The 40 % concentration is the one I elected to use clinically for compressing and soaking, for higher strengths seemed to exert no greater effects. Robinson's (5) use of 2 % solutions of urea for purulent conditions would seem to be far below that required for either the lytic or bacteriostatic effects, and I contend strongly against his claim of a direct stimulating action on healing through promotion of granulation tissue. Apropos of this, it is hardly likely that the concentration of urea in urine, which is not ordinarily in excess of 2 %, furnishes a modern proof of the therapeutic validity of the ancient practice, dating from the Babylonians, of instilling urine into wounds, though assuredly the quaintness of this procedure and the possibility of ingenious modes of applying exquisitely fresh solutions cannot be held to be without any kind of effect. Robinson (5) maintains that the favorable effect of maggots in cleaning up dirty wounds is due to their excretion of allantoin which yields urea on hydrolysis, and that the latter agent is, therefore, the praiseworthy element in this, happily now obsolete, therapy.

3. Other properties.

Urea accelerates the digestion of fibrin by trypsin and pepsin at an optimal concentration of about 15 % (6), but since higher concentrations are inhibitory, any beneficial effects of high concentrations probably cannot be attributed to this particular property. It is mildly keratolytic but not sufficiently so to be of real clinical use. Before anyone has a chance to be intrigued by the fact that urea is both keratolytic and antifungal, I should like to remove all doubt about its effectiveness in ringworm infections: its worthlessness in this respect is not exceeded by any other agent, active or inactive. It is highly soluble in water. It is not toxic even when liberal amounts of the crystals are poured directly onto inflamed skin or into wounds though in such amounts it may sometimes cause stinging and pain. The presence of crystals does not prevent skin grafts from taking, a good indication of harmlessness (1). The deodorizing of stinking, foul lesions is one of urea's outstanding virtues which has recommended it, at least in the past, to the attention of surgeons. Holder and MacKay (7) were impressed with this capacity and I heartily endorse their recommendations. Doubtlessly, the deodorization is chiefly due to the suppression of bacterial overgrowth.

Clinical applications

Urea has been advised for many types of suppurative lesions, for example: suppurative otitis media, infected wounds, purulent ulcers of all varieties, necrotic neoplastic growths, osteomyelitis, carbuncles, burns, etc. (8, 9). Rattner (10) suggested a combination of 5 % each of urea and sulfathiazole for pyoderma, but topical use of sulfathiazole is passe and besides 5 % urea is

well below the effective concentration. Perhaps urea would have been destined for a widespread use topically had not the successes of modern chemotherapy, beginning with the sulfonamides, proved so brilliant, instantly rendering obsolete older, and less spectacular remedies. There still remains, however, certain circumstances in which the use of urea would seem advantageous. I have reference especially to its use as a dermatologic compress or soak, though this particular application seems to have received little or no attention. Of course, it is a mischievous maxim among the sophisticates of dermatology that agents for compressing and soaking should *sting*, *stink* or *stain*; patients at least are thought sincerely to admire these properties, and it is a fact that physicians are devoted to gratifying patients' needs. Some cynics have had the audacity to consider whether water is not really the "active" therapeutic agent in the standard compresses containing potassium permanganate, aluminium subacetate, (Burow's Solution), and the like. Perhaps it is futile to consider that an agent such as urea could find acceptance when it neither discolors the skin, has no strong odor and cannot even be felt — in short, has none of the virtues which in the popular mind is connected with effectiveness. Its cheapness is perhaps another point against it, not to mention its vulgar associations.

After using 40 % urea compresses and soaks for several years in an unrecorded number of patients with many different cutaneous afflictions, I have the strong impression that these are advantageous for inflammatory lesions which present elements of exudation, suppuration and crusting, especially when there is evidence of secondary infection. It is the "dirty" lesion, regardless of origin for which urea is suited. I shall not contend that this view is proved beyond doubt since I performed no controlled experiments. Furthermore, urea has no superiority over water, or the traditional agents commonly dissolved in water, boric acid, aluminum acetate, potassium permanganate, etc., when applied to a "clean", acute, self-limited dermatitis which is not secondarily infected or crusted.

The conditions for which urea solutions can be advised, providing, of course, the above specifications of a "complicated" dermatitis are met, include: contact dermatitis preeminently, burns, impetiginized eruptions (pyodermas), nummular eczema, various kinds of hand and foot dermatitis, and indeed any eczematous process in which suppression of bacteria and debridement appear desirable upon inspection of the clinical characteristics. Obviously, if the lesion is of the kind which will not heal spontaneously, when it has been "cleaned up" by soaking and compressing, complete cure is not to be anticipated though there may be amelioration. Secondarily infected nummular eczema, for example, will be benefited initially, but the underlying process ordinarily continues after the superimposed disturbances have been cancelled out. For the primary pyodermas, impetigo, ecthyma and the like, antibiotic ointments are clearly superior; they are neater, easier and achieve quicker results. Neomycin compresses (0.1 to 1 %) are highly useful for infected dermatitides but lack lytic effects on accumulated debris, other than that brought about by the water, of course. Urea solutions may be used over and over again until the solution becomes too "dirty" for the patient.

As part of this study, a preparation containing 40 % urea in Carbowax ointment was applied more or less indiscriminately to the common dermatoses

encountered in private practice, but no effects were observed which would warrant further interest. Small concentrations of urea, 5 % and less, are increasingly being incorporated into various cosmetic preparations but the value of this is unauthenticated. Rattner (10) thought 3 % urea in a vanishing cream base to be a worthwhile type of hand cream for every day use.

Finally, I would reemphasize the value of urea for the initial local treatment of suppurating wounds, necrotic malignancies, foul ulcers with a purulent slough, and similar lesions. Of course, parenteral antibiotics should not be neglected where indicated. The crystals may be liberally sprinkled into the lesion which is then covered with a sopping wet aqueous compress to effect solution or a 40 % compress may be applied directly. Maintained for 20—30 minutes and repeated several times daily, a striking deodorization may be achieved as well as a variable reduction in the accumulated discharge and slough. Strepdodornase — streptokinase combinations (Varidase) are, in my experience, generally superior to urea, achieving a higher degree of debridement in a shorter period, but often the final result is not so much more striking. The same may be said for trypsin debridement. Neither of these agents are antibacterial, and their deodorizing abilities are consequently far less notable.

SUMMARY

Strong solutions of urea, 40 % and over, are useful in the treatment of inflammatory skin lesions accompanied by exudation, suppuration and crusting. The value of urea in the deodorization and debridement of suppurating wounds, suppurative ulcers and necrotic malignancies is reemphasized.

RÉSUMÉ

Des solutions concentrées d'urée, 40 % et plus sont utiles dans le traitement d'affections cutanées inflammatoires avec exsudation, suppuration, et formation de croûtes. On insiste encore sur la valeur de l'urée comme désodorisant de même que pour le nettoyage de plaies purulentes et d'ulcérations nécrotiques.

ZUSAMMENFASSUNG

Starke Lösungen von Harnstoff, 40 proz. und stärker, sind bei der Behandlung entzündlicher Hautaffektionen mit Nässen, Eiterung und Krustenbildung von Nutzen. Der Wert des Harnstoffs als Desodorans sowie zur Reinigung eiternder Wunden, eitriger Geschwüre und nekrotischer Geschwülste wird nochmals betont.

RESUMEN

Soluciones de urea, fuertes, al 40 % y más, son de uso corriente en el tratamiento de lesiones inflamatorias de piel acompañadas de exudación, supuración y costras. La utilidad de la urea como desodorante y en el desbridamiento de heridas supuradas, úlceras supuradas y necrosis de lesiones malignas, es recomendable.

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