Special Communication

PVP: IN GASTROENTEROLOGY

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Polyvinylpyrrolidone (PVP) was developed as a plasma expander in the early 1930's and was first used medically during the second world war as a colloidal component of the plasma substitute periston (Hecht and Weese, 1943) to treat haemorrhagic and traumatic shocks. In addition to being a colloid, PVP also binds to various macromolecules, such as dyes (Bennhold and Schubert, 1944; Bennhold et al., 1950; Scholtan, 1953) and toxins (Dieckhoff and Kuenstler, 1943; Bovet et al., 1947; Schubert, 1948) whereby it comes close to what could be termed a 'synthetic protein'. In more recent years, PVP has been used clinically and experimentally to measure glomerular permeability (Scholtan, 1959; Hecht and Scholtan, 1959, Hardwicke et al., 1968; Hulme and Hardwicke, 1968; Arisz et al., 1969), the permeability of the gastrointestinal tract to circulating macromolecules (Gordon, 1959; Jarnum, 1961; Fell et al., 1969; Hardy, 1969; Clarke and Hardy, 1969; Clarke and Hardy, 1969) and the capillary transfer of macromolecules from the intravascular space (Vogler and Strucker, 1964).

In gastroenterology PVP has been used from 1960 onwards to an increasing extent to diagnose enteral protein loss. During exudative processes in the gastro-intestinal tract albumins are eliminated into the intestines. At first the attempts were made to determine the amount eliminated by injections of radioactive marked albumin. The technique was later rejected by some authors (Jeejeebhoy 1961). This is where the low molecular PVP can be made use of, as it has more or less the same molecular weight as albumin, and resist digestive ferments. The radioactive marking of PVP is either made by binding tritium (^{3}H) or ^{14}C respectively directly with the PVP molecule or by adsorptive binding of foreign elements ^{131}iodine (^{131}I) or 31Cr. As the chemical binding of tritium or ^{14}C is technically demanding and expensive, mostly the absorptive ^{131}I coupling has been prefered (Martini et al., 1960; Barandum et al., 1963; Gordon, 1961; Dawson et al., 1961). After the intravenous injection of PVP-^{131}I the stools are collected for three to four days and the radioactivity is measured. This gives the basis for the amount of PVP excreted by exudation into the intestines. The PVP is also a basis of measurement for the albumin excreted. This method occasionally referred to as the Gordon test has a number of sources of error, which have been occasionally referred

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The ^{131}I can dissociate and possibly be reabsorbed. The measured values of radioactivity would accordingly indicate too low a PVP or albumin exudation respectively. Moreover there is a danger that the injected iodine would immigrate into the iodine-storing or iodine-metabolizing organs, above all into the thyroid. For this reason it is necessary to saturate the organism with iodine before the I-PVP test. Because of the sources of error and the difficulties mentioned some authors prefer ^{51}Cr-chloride or albumin-^{51}Cr to ^{131}I-PVP (Wessel et al., 1971). The reabsorption of the tracer should be prevented by ion exchangers, such as amberlite.

Schedl and Clifton (1962) drew attention to the fact that a strong binding of PVP to mucus substances of the intestinal mucosa and the retention connected with it must be considered a source of error. Normally Ca. 0.3% of the intravenous injected PVP doses are excreted in the stools of healthy persons (Bosseckert and Keil, 1962). The passage of plasma into the intestine should take place in the border area of duodenum and jejunum. An excretion of more than 3% of PVP indicated exudative processes of the intestinal mucosa.

A catalogue of syndromes with increased PVP or albumin excretion was made by Dawson et al. (1961). In it the exudative enteropathy with consecutive hypoproteinaemia is most important. Secondary, all inflammatory changes of the intestinal mucosa covering a large area, such as enteritis regionalis and colitis ulcerosa are mentioned.

Tumors of gastro-intestinal tract also lead to increased PVP excretion and corresponding enteral albumin loss. Disturbances of the lymph flow, blockages of the ductus thoracicus and dextrocardiac insufficiency with venous congestion likewise have a positive result with the Gordon test.

In some cases of "essential or idiopathic hypoproteinaemia", an increased enteral albumin excretion was detected by means of a ^{131}I-PVP injection (Martini et al., 1960).

In experiments on mice Witschi et al. (1962) could produce an increased protein excretion in the intestines, by X-ray radiotherapy of the whole body with 800 r, which corresponded exactly to the picture of an exudative enteropathy in man and showed an increased exudation of ^{131}I-PVP in the Gordon test.

At the same time the additional injection of ^{131}I-triolein showed that not only hydrosoluble substances but also lipid pass the intestinal wall and reach the lumen.

The intestinal absorption of ^{131}I-PVP has been measured in unsuckled conscious pigs of less than 20 hours old by the measurement of the concentration of ^{131}I-PVP in venous blood during the six hours after feeding and also by the distribution at the end of experiment of ^{131}I-PVP between homogenates of the alimentary tract and homogenates of the rest of the animal. The concentration of ^{131}I-PVP in the peripheral blood after feeding was dependent upon the molecular weight of the polymer, when comparable amount has been absorbed from the intestine. PVP K-60 attained higher blood concentration than PVP K-30 and the blood concentrations of PVP K-60 were close to the values to be expected if all the material which had left the intestine has remained in the blood. The lower blood concentrations found when PVP K-30 was fed, were associated with the disappearance of labelled solute from the gut and were consequence of the relatively rapid escape of labelled solute from the plasma after absorption had taken place.

The ability of the intestine to absorb ^{131}I-PVP K-60 declined progressively after birth but did not terminate abruptly unless the animal was fed in colostrum. In unsuckled animals the rate and extent of absorption at 3 hour was much greater than at 20 hours after birth but some absorption was still present at least 65 hours after birth. The absorption of ^{131}I-PVP K-30 was found to be much less dependent upon the composition of the solvent than the absorption of ^{131}I-PVP K-60, although absorption was most rapid when PVP K-30 was fed in colostrum (Hardy 1969).

The absorption of labelled PVP by the intestine of young rat has also been studied by ^{125}I-PVP, in which PVP uptake was never seen in the duodenum and became restricted to the distal half of the small intestine by the 18th day of life. In animals between 18 and 20 days old the uptake of the PVP declined progressively until, in animals more than 20 days old, less than 5% of the radio-activity was taken up by the intestinal wall (Clarke and Hardy, 1969). The subsequent decline to zero in uptake was due to an almost uniform decrease in PVP uptake by the distal half of the small intestine.

Histological studies indicated that rapid decline in PVP uptake did not reflect a decrease in uptake by individual cells, but rather their replacement by new cells incapable of taking up PVP.

Auto-radiographic estimates of turnover time in the intestinal epithelium using tritiated thymidine reveal good agreement between the time needed to replace completely the epithelium of the ileum (62 hr) and the duration of the rapid decline in PVP uptake (approx. 3 days).

It seems that on or about the 18th post natal day there is an abrupt change in the functional characteristics of the apical plasma membrane of cells produced by the crypts of Lieberkuhn in the distal half of the small intestine. The stimulus for this change is unknown, but cells produced subsequently cannot take PVP (Clarke and Hardy, 1969).

Macromolecular absorption in the new born animals is a phenomenon of considerable physiological and immunological interest, but there are severe limitations to its investigation with antibodies or other protein species (Brambell 1966; Hardy 1969).

Of special interest is the observation by Hazenberg et al. (1969) that an enteral albumin exudation not only occurs in primary pathological changes of the gastro-intestinal tract mentioned, but also secondarily in the nephrotic syndrome. The demonstration of these casual relationships was only made possible by the ^{131}I-PVP test. Hazenberg et al (1969) assume that the loss of protein through the intestines with renal proteinuria is causatively due to an edema of the intestinal mucosa.

There has been report on cases of long term diabetes with glomerulosclerosis which likewise proceed with a considerable increase of an enteral protein excretion. At the same time the authors emphasize that the test substances marked with tritium are considerably more stable and the test results are more reliable than with ^{131}I-PVP.

Following the intravenous administration of a dose of ^{131}I-PVP, the radioactivities in the plasma and in the total body decrease at distinctly different rates. This behaviour is a consequence neither of the polydispersity of ^{131}I-PVP nor of equilibration between intra and extra vascular spaces, but of uptake of labelled particles by reticuloendothelial cells. This inference, which directly follows from the work of Ravin et al. (1952), is verified by the domonstration that the rate of elimination of PVP from the circulation is altered in a variety of conditions without any concomitant changes in the ^{131}I-PVP activity of the whole body.

The difference between these two rates is utilized to calculate the phagocytic rate of ^{131}I-PVP by reticuloendothelial cells. A number of experimental conditions are reported in which enhanced reticuloendothelial uptake of ^{131}I-PVP is readily demonstrable. They include the injection of small quantities of heterologous plasma, certain proteolytic fragments of the fibrinogen molecule, the clearance of antigen-antibody complexes, and the acute phase reaction (inflammatory response) as brought about by serum sickness, sterile abscess and vaccination.

Based on these observations it has been suggested that ^{131}I-PVP may provide a convenient technique for the long term monitoring of the activity of reticuloendothelial cells, presumably mainly that of the histiocytes. The pronounced polydispersity of commercially available ^{131}I-PVP is a serious problem in this respect which can be largely overcome, but not completely abolished, by various screening techniques.

Due to the relatively low affinity for phagocytic cells, ^{131}I-PVP disappears from the circulation rather slowly and thus provides a convenient way to followup the duration and extent of enhanced phagocytic activity in pathological states.

The consequence of the polydispersity of ^{131}I-PVP are two fold. First, the majority of the small polymers is rapidly eliminated through the kidney and secondly, the remaining heterodisperse polymer population is phagocytized in an inverse order of molecular weight. The comparatively higher affinity of the smaller polymers for phagocytic cells can be demonstrated by the re-injection of excreted ^{131}I-PVP.

According to Janeso (1955) PVP is taken up by the reticuloendothelial cells in body-wide distribution. Nevertheless, it should not be overlooked that the tissue distribution of ^{131}I-PVP is fundamentally different from that of some other macromolecular complexes, for example the 2-macroglobulin/Subtilisin A complex (Debane et al., 1973). Indeed the high radioactivity content of skin and muscles (the later presumably located in interior muscular fasciae rather than in muscle fibres) Regoeczi (1976) suggests that ^{131}I-PVP has a higher affinity for histiocytes than for the reticuloendothelial elements in the immediate vicinity of the circulation (e.g. Kupffer Cells, Splenic and Pulmonary macrophages). Similar distribution of ^{14}C-PVP was reported by Ravin et al. (1952) for the tissue of man and rat. Finally it is noteworthy in this connection that according to several reports (Schoen, 1949; Ammon and Muller, 1949) infusion of PVP in large doses provokes histiocytosis. All this point to the existence of an intimate relationship between PVP and histiocytes and to the possibility that ^{131}I-PVP may be a tracer of histiocyte activity in the first place.

The experiments described by Regoeczi (1976) show that the "normal "rate of uptake of ^{131}I PVP by the reticuloendothelial system (RES) can be modified in more than one way, but the underlying molecular mechanisms are obscure. If extracellular PVP exists in the body fluids free of any associations with other macromolecules (plasma proteins) then enhanced phagocytosis of ^{131}I. PVP is likely to be secondary

phenomenon arising from the increased endocytic activity of cell membranes for which it has an affinity. Alternatively it is possible that PVP exists in vivo in association with one or more plasma constituents, in which case increased phagocytosis of ^{131}I-PVP would signify a change in the turnover of these components. The possibility that PVP forms complexes with albumin (Hecht and Scholtan, 1959) and fibrinogen (Fletcher et al., 1952; Perkins et al., 1966) has been pointed out before. These observations made either with purified proteins or under conditions favouring cryoprecipitation, and different test systems employed in such studies failed to produce similar results. For this reason the precise nature of the mechanism, which is capable of transporting PVP into reticuloendothelial cells remain unknown.

PVP Carcinogenesis

Since the Hueper's publication (1957) "Polyvinylpyrrolidone a carcinogenic agent for rats" the question of the carcinogenic effects of PVP has been repeatedly discussed (Najma et al., 1968; Ashwood Smith, 1971; Strif et al., 1977).

Hueper had implanted various PVP fractions of molecular weight 10,000—300,000 in rats, mice and rabbits and could thereby only produce sarcomas at the site of implantation in rats. In a later series of tests he gave the same PVP fractions intravenously and obtained again only in rats reticulosarcoms. In another study Hueper (1959) stressed that after PVP application sarcomas occurred at the injection sites and in the storage place.

In experimental pathology it is well known that rats are especially susceptible to carcinogenic agents, which in fact led to the term "Sarcoma animals". In certain rat strains sacromes can develop after almost any noxa. Thus Notholruft (1955) showed that in some strains of rats implanted foreign bodies such as gold, silver, ivory, platinum, polystyrol, cellulose and polyvinyl chloride cause sarcomes and carcinomes. Evidently Hueper had used in those tests strains of rats which were particularly susceptible, so that noxa which have no carcinogenic effect in other strains of rats and other animal species already led to the formation of malignant tumors. In this way it must also be explained that Hueper's findings could not be confirmed in numerous PVP tests on rats.

In addition Hueper (1961) reported PVP tests on rats in which spontaneous mammary tumors were inhibited in growth by PVP 50,000. These tests showed, in contrast to the earlier tests, the opposite effect so that Hueper talks of an ambivalent carcinocid-carcinogenic effect of PVP.

Although PVP-iodine absorbed from the peritoneal cavity may be lethal in the rats (Lavigne et al., 1974) but clinically in man no toxic effects have been reported (Lavigne et al., 1974; Feldtman et al., 1975). The high level of peritoneal absorption noted in man (Strif et al., 1977) and in rats (Lavigne et al., 1974) and the potential toxicity of PVP-iodine absorbed from the burn areas (Pietsche and Meakins, 1976; Lavella et al., 1975) suggested the limitation of its intraperitoneal use, until some clear evaluation emerges from the present day research.

It is noteworthy to mention here that in a recent study (Wlodkowski et al., 1975) the DNA modifying and mutagenic activity of PVP-iodine in a widely used topical antiseptic for microorganisms has been reported. Such an effect has been shown to occur also in mammalian cells growing in culture. The observation that the PVP-iodine induced lesion is repairable upon incubation in the absence of the agent indicates that this degradation of the DNA is specific and does not reflect a general toxic effect of PVP-iodine resulting in autolysis. Because studies on the interaction of PVP-iodine with purified DNA have not indicated a DNA degradation, it may be postulated that the degradation seen in vivo is a reflection of an initial step of an enzyme DNA excision-repair process, presumably involving the removal of a PVP-iodine modified base, most likely 5—iodo-cytosine (Speak et al., 1976).

Meanwhile long term trials have also been carried out by several authors with various PVP fractions not only on rats, but also on mice, guinea pigs, cats and dogs, without succeeding in producing malignant tumors.

Uptil now, likewise no carcinogenic effects of PVP in man have been known. At least 500,000 persons have received PVP infusion in last 30-35 years, we would expect a massive rise in sarcoma or carcinoma cases respectively in this group of people if PVP had a carcinogenic effect. A significant and more frequent occurrence of malignant tumors has not, however, occurred in these people treated with PVP, although the latency period has meanwhile been exceeded. As Hueper sees a casual relationship between the development of tumor after PVP and the storage there would be no danger of a carcinogenic effect in the low molecular PVP fractions (11500-20,000) as they can pass the kidneys and can be quickly eliminated. The best proof against the carcinogenic effect of PVP is given in the cases of "PVP Storage disease", as discussed earlier (Najma et al., 1978) in which doses from 2-3 Kg of PVP 50,000 were injected within the course of 14-20 years. In those cases although dermatosis, rheumatic joint complaints and pulmonary changes with increasing respiratory insufficiency

occurred, malignant tumors were not found in any of the cases (Wessel et al., 1971). These studies reveal that there is no carcinogenic effect to be expected from PVP in man, at least in the PVP fractions below molecular weight 50,000.

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