Progress report

Carbenoxolone sodium

A large number of substances can be extracted from liquorice root. One of these is glycyrrhizic acid and the aglycone of this is glycyrrhetinic acid. Carbenoxolone sodium is synthesized from glycyrrhetinic acid and is the di-sodium salt of 3-0-(β carboxypropionyl)-11-oxo-18β-olean-12-en-30-oic acid. Its pharmacological actions are entirely different from both glycyrrhetinic and glycyrrhizic acid. A comprehensive review of the drug, its action and its therapeutic use, covers information available to June 1970.1 This report will be mainly concerned with further experience and will try to summarize in certain areas the total experience since the drug was introduced in 1959.8

Mechanism of Therapeutic Effects

These appear to be multifactorial and relate to alteration in the rate of cell turnover, in the physico-chemical characteristics of mucus, and, to a lesser extent, the production of H ions.

Progenitor cells of the gastric and duodenal epithelium lie in the neck and isthmus, giving rise also to xymogenic cells, but more slowly. The life of mucus cells is a few days so that both morphological and biochemical changes occur rapidly as they move from the neck towards the surface.

The protein component of mucus originates in the ribosomes of the endoplasmic reticulum and from there is transported to the Golgi complex, where condensation, sulphation, and carbohydrate addition bring about the formation of the protein-polysaccharide complex which is a mucinogen granule. On discharge from the cells these granules may stay attached to the surface lipoprotein cellular membrane or float out into the paramucosal lumen of the alimentary tract and from there admix with gastrointestinal luminal contents.

Effect of Carbenoxolone on Cell Life

In the normal situation control is exerted over these developments by a repressor or inhibiting factor aimed, by reducing DNA effectiveness in mitosis, at cell replication (it is one of the homeostatic forces that appears to be lost in cells undergoing neoplastic proliferation), and the precursor of nucleic acid, thymidine kinase, is particularly inhibited. Using isotope-labelled titrated thymidine with the DNA content and radioactivity of the gastric mucosa as indicators of the rate of removal of proliferating epithelial cells, a gross difference occurs in the mucosa of control animals from those pretreated for two weeks with 6-10 mg/kg body weight of carbenoxolone sodium.8 At the site of maximal absorption of the agent, in the stomach, carbenoxolone increases the life span of the cells by approximately 50%.

In a comparison of the rates of proliferation and extrusion of epithelial cells in the rodent under restraint stress for 48 hours, while the rate of cell loss is unchanged there is a significant decrease in the rate of proliferation. When rats are pretreated with carbenoxolone sodium, the rate of removal of labelled...
cells is significantly less than in untreated controls. Higher specific activity is obtained in the stress-restrained animals than in controls, indicating that the turnover rate of epithelial cells is decreased both by carbenoxolone and by stress and more so when both are combined. This decrease leads to an increase in the life span of the epithelial cells.4

Carbenoxolone and Mucus

Accompanying the prolongation of cell survival are parallel changes in the volume of mucus extruded. It is speculated, but not yet known, that carbenoxolone acts by inducing the enzymes of mucoprotein synthesis. If this proves to be the case, it could also be interfering with the enzymes which determine cell differentiation. Parke6 suggests that as carbenoxolone must pass through the cells of the gastric mucosa during the process of absorption, it becomes associated with a number of proteins within these cells, including interaction with functional proteins such as the nuclear histones which regulate the metabolic activity of the cells and, in particular, the synthesis of glycoprotein.

Topical application of carbenoxolone sodium to the mucosa of a canine denervated gastric pouch results in a considerable increase in the secretion of mucus.8 During experiments on the movement of sodium and hydrogen ions through the gastric mucosa a pouch is irrigated with bile or with inactive control solutions. A significantly greater secretion of mucus occurs when 100 mg of carbenoxolone sodium in 30 ml is allowed to remain in the pouch for one hour before exposure to either bile or the control solutions. Bile irrigation is accompanied by marked loss of hydrogen and sodium ions from the pouch whereas in control experiments the loss of hydrogen ions is small and sodium tends to move from the pouch into the mucosa. Where bile irrigation is subsequent to the hour's topical application of carbenoxolone, the loss of hydrogen ions does not occur though the loss of sodium ion into the drainage is similar to that in the controls. This is the first time that any agent has been shown to increase the resistance of the mucosa to penetration by hydrogen ions and also to protect it from the damaging effect of bile. The apparent selectivity of carbenoxolone in blocking the movement of hydrogen ions must, speculatively, at present, be attributed to the increased secretion of gastric mucus.

This experience is not universal. Thus Maiwald and Weicker,7 observing 24 patients with either gastritis or gastric ulcer being treated with a four weeks' course of carbenoxolone, found the total amount of mucus and the albumin portion in aspirated gastric juice before and after stimulation with betazole were both lowered.

The concentration and total amount of polysaccharides in rat gastric juice significantly increased after carbenoxolone in a dose of 100 mg/kg body weight.8 The non-dialysable content of the gastric juice is increased by 300%. Of the sugar components, fucose, D-glucose, and acetylmuramin acid are unchanged, but a proportionate increase occurs in the D-mannose, the D-galactose, and the D-hexosamine. Though the total volume of the gastric juice fell, hydrochloric output is unchanged, the concentration increasing proportionately. An increase was observed in the PAS-positive material, the mucus on the surface of the gastric mucosa, and also in the crypts. Pre-treatment with carbenoxolone prevented the appearance of deep gastric ulceration in rats under restraint compared with a 70% incidence in controls.
Pretreatment with carbenoxolone protects human gastric mucosa from damage by pickles.9

Further evidence that carbenoxolone may alter the balance of the different sugars in mucus has been provided by Schrager.10 A patient grossly disabled by severe mucorrhoea due to Pneumatosis cystoides intestinalis had repeated courses of oral carbenoxolone sodium in a dosage of 200 mg/day. On this regime, three formed bowel motions were passed in 24 hours, containing obviously tenacious mucus. On each occasion that carbenoxolone was stopped mucorrhoea recurred within a few days and the bowel was evacuated between 10 and 20 times in 24 hours. Large gut mucus differed in composition from gastric and salivary mucus by a longer carbohydrate side-chain similar to that present in the mucus of bile. Carbenoxolone alters the balance of galactose to glucosamine and galactosamine in colonic mucus and, furthermore, the concentration of the mucus per volume of stool becomes significantly greater. This raises the possibility that though the greater part of the faecal excretion product in man is carbenoxolone-30-glucuronide, when this is attacked by the gut flora it may not all be hydrolysed to B glycyrrhetic acid, as discussed later, but that some carbenoxolone may become unbound and have a topical action on the mucosa of the colon. Thus carbenoxolone could influence ulcer disease both by alteration in the nature and volume of the mucus secreted as well as by prolongation of the life of the mucogenic cell. These would serve to protect the breach in the mucosa from further damage, either by proteolytic agents or by hydrogen ions.

**Carbenoxolone and Pepsin**

There remains some uncertainty as to whether ulceration in the gastric mucosa is dependent more upon the secretion of pepsin in the presence of a suitable acid milieu than upon the ability of hydrogen ions to penetrate the gastric mucosal defence mechanisms.11 Inhibition of peptic activity by carbenoxolone accompanies substantial reduction in the secretion of hydrogen ions by the parietal cells in pylorus-ligated rats pretreated with carbenoxolone.12 The significance of the fall in the histamine-stimulatated maximal secretory capacity of the stomach in carbenoxolone-treated patients is uncertain.13 If this observation can be confirmed, a reduced production of hydrogen ions could influence the proteolytic performance of pepsin I, the optimum pH of which lies between 1·5 and 2·7. However, while pretreatment with between 12·5 mg and 200 mg/kg of orally administered carbenolone to ligated pylorus rat preparations has no effect on the volume of secretion, progressive inhibition of pepsin activity occurs, which is total at the highest dosage.12 Glycyrrhetinic acid, the parent substance for carbenoxolone, has less antipepsin activity and does not influence the secretion of hydrogen ions. Two mechanisms occur which could explain the inactivation of pepsin: the raising of the pH of the secretions and the binding of pepsin to the carbenoxolone molecule since pepsin is an albumin and the affinity of carbenoxolone to albumin in the plasma is avid. In chronic in-vivo rat experiments Henman also compared the effect of feeding 10 mg/kg of carbenoxolone, a solution of sodium bicarbonate, and the same dose of carbenoxolone to which is added 2·5 mg/kg of spironolactone. After 17 days the pylorus was ligated in some of the animals and, compared with the control bicarbonate-treated rats, the other two groups show a significant reduction of pepsin concentration,
the largest being in the group having spironolactone. After 23 days only rats treated with both spironolactone and carbenoxolone showed a significant depression of peptolytic activity. Carbenoxolone proved to be a more effective inhibitor of proteolytic activity than Roter (a patent acid-buffering mixture of bismuth subnitrate, magnesium carbonate, and sodium bicarbonate) and also of a degraded carregeenan product (Ebinar). Parallel studies in vitro emphasize the dose dependency relationship with total inhibition of digestion of a plated haemoglobin substrate by 10 mg of pepsin when 250 mg of carbenoxolone was added. In the clinical situation, however, the addition of spironolactone to antagonize the mineralocorticoid effect of carbenoxolone appears to cancel out the ulcer healing properties. The antipepsin potentiality of carbenoxolone remains to be examined in humans.

To summarize, carbenoxolone sodium appears to be an agent capable of stimulating the elaboration and secretion of mucus, changing its molecular construction, inhibiting pepsin, prolonging the life of migrating epithelial cells and, finally, of opposing the destructive properties of bile upon the gastric mucosa. Thus this appears to be an agent which is theoretically capable of influencing both sides of the ulcer equation of acid + pepsin = mucus + cells to the advantage of ulcer subjects.

Carbenoxolone in the Treatment of Gastric Ulcer

From 1962 to 1969 the therapeutic effect of carbenoxolone has been reported in a total of 492 patients with gastric ulcer, mainly in patients who are ambulant but also, in four trials, where they remain in hospital. In all of these 14 trials, the drug was shown to be beneficial. In one trial, which was uncontrolled and contained only eight patients, no benefit was observed. Most workers treat their patients with 300 mg carbenoxolone sodium daily for one week, subsequently dropping this to 150 mg. In recent reports adverse side effects requiring cessation of therapy are not described. Stadelman and his colleagues treated 41 patients with gastric ulcer, utilizing a double-blind control method, the patients remaining ambulant. Of 29 carbenoxolone-treated ulcers, 13 had healed completely at the end of four weeks, as compared with four out of 12 controls. Another 14 carbenoxolone-treated patients showed significant reduction in the size of the ulcer as compared with four of the controls. Von Schiemann, utilizing serial endoscopic observations of 33 patients with gastric ulcer who had previously shown no response to conventional therapy, found that after four weeks on carbenoxolone sodium 16 had healed and six were significantly reduced in size. By eight weeks, 21 had healed and nine had significantly reduced in size. Eight of 12 cases of gastric ulcer which had proved resistant to conventional therapy healed within six weeks as determined by endoscopy. Thus the trials reported from other European countries confirm the finding of Doll and his colleagues 10 years ago.

Because of the tendency of carbenoxolone sodium to give rapid symptomatic relief, the possibility arises that surgery may be delayed in the management of malignant ulcers, where such lesions have not been identified by endoscopy and biopsy. Of 76 patients initially diagnosed with benign gastric
ulcer and treated with carbenoxolone, observation of up to five years showed only two patients to have malignant ulcers. Both were recognized by repeated radiology within three months of the onset of treatment.\textsuperscript{35}

**Carbenoxolone in the Treatment of Duodenal Ulcer**

Because of the evidence that the beneficial effect of carbenoxolone sodium in the treatment of gastric ulcer is a function of contact with, and absorption through, the mucosa, after a favourable initial pilot study in which carbenoxolone sodium was dripped directly into the duodenum through an intra-alimentary tube to the area of duodenal ulcers, a gelatine capsule was devised to rupture in the antrum within the time of one half to two hours from ingestion and contained 50 mg of carbenoxolone sodium with sugar tartaric acid and sodium bicarbonate. Capsules appeared to rupture at the pylorus in approximately 75\% of instances\textsuperscript{36} and using \textsuperscript{14}C-labelled carbenoxolone with barium sulphate in the capsules, three out of four burst in one and a half and two and a half hours of ingestion.\textsuperscript{37} As could be anticipated, the maximum blood level after ingestion of carbenoxolone capsules occurs between three to five hours later, as compared with the maximum at one to two hours when plain carbenoxolone sodium is absorbed from the stomach. Early trials with this capsule reported favourable results, but lacked controls.

In a British multicentre trial of 115 ambulant patients with duodenal ulcer, a group of 60 received carbenoxolone sodium in the delayed-release capsule and a group of 55 received a placebo capsule identical in shape and appearance with the active one. The patients were allowed to take alkaline tablets whenever they had pain and recorded the number taken each week. The carbenoxolone sodium was given in a dose of 200 mg a day for two months and thereafter 100 mg a day for a further four months. A statistically significant smaller number of patients on the active capsules took fewer alkalis than those in the control group. Of 23 patients who showed a definite ulcer crater in the duodenum at the onset of the trial, at a repeat of the examination six months later, only two still showed an ulcer crater. Of 14 patients from the control group with repeat radiography at six months, seven still showed a crater. The difference was significant at a probability less than 1 in 100.\textsuperscript{38} In another study, however,\textsuperscript{39} 94 patients with duodenal ulcer were divided into three groups. Fifteen had the standard commercial carbenoxolone sodium delayed-release capsules, 33 received the active drug in a specially identifiable capsule, and nine controls received capsules with inert contents. After one month a radiologically identified ulcer crater had disappeared in three quarters of patients in all three groups. In this study the patients were on bed care in hospital and in this situation carbenoxolone sodium seems to have only marginal value as compared with its use in the ambulant patient. In a small double-blind trial in Nigeria, 14 patients received carbenoxolone sodium delayed-release capsules for more than nine months.\textsuperscript{40} Fourteen patients started with the active capsules and another 14 were changed over to them after a period during which no improvement had been obtained using conventional methods of treating duodenal ulcer. Of these 28 patients, at six months the radiologically identified ulcer crater had healed in 12, improved in another 10, but had not changed in six. Sodium sesquicarbonate, added to foodstuffs in that country and also to powdered tobacco for use as a snuff, contains a large amount of potassium which may account for the absence of
any potassium depletion. In a double-blind trial of the carbenoxolone sodium capsules, in 50 patients with duodenal ulcer after four weeks radiological improvement was observed in 21 of 25 patients on the active capsules and in nine of 25 on the placebo.\footnote{41}

**Carbenoxolone and Maintenance Therapy**

In a double-blind study in South Africa, a daily dose of 200 mg was given for six months. At the end of this period 12 of 28 duodenal ulcers had healed radiologically, 10 improved, but six were unchanged. Gastric ulcer patients received 150 mg a day and recurrent or continued ulceration was present at the end of 12 months in 17\% as compared with 38\% of controls. At the end of 18 months 25\% had a recurrence or continuation of activity of the ulcer as compared with 46\% of controls.\footnote{48} None of these patients developed oedema, hypernatraemia, or hypokalaemia.

The overall impression remains that the drug is most effective in the ambulant patient, provides for earlier healing of both gastric and duodenal ulcers but that its role in maintenance therapy and in prophylaxis requires further study.

**The Use of Carbenoxolone in Other Conditions**

A mixed bag of disorders in which benefit is ascribed to carbenoxolone includes recurrent aphthous ulceration of the mouth,\footnote{43} periadenitis mucosae necrotica recurrens,\footnote{44} reflux peptic oesophagitis,\footnote{45} herpes simplex,\footnote{46} and balanitis.\footnote{47} Each of these reports requires confirmation. In ulceration of the mouth due to emepronium bromide,\footnote{48} pellets of carbenoxolone sodium reduced healing time by more than 50\% in 17\% of 76 elderly patients who had received Cetiprin for incontinence. The mouth ulceration was caused by prolonged contact of the agent with the buccal mucosa as a result of failure in these mentally impaired individuals to swallow the tablets.

**Pharmacology and Biochemistry and Adverse Reactions**

The described side effects of the drug are sodium retention, hypokalaemia, and myoglobinuria.

**THE MECHANISM OF THE SODIUM RETENTION**

Concentrations of aldosterone down to 3.5 × 10^{-7} M enhance sodium transport through toad skin membranes.\footnote{49} Carbenoxolone alone has no effect but when applied either before or simultaneously with the exposure to aldosterone, a synergistic effect is obtained. This appears to be specific as carbenoxolone has no influence on the effect of vasopressin on transport. Two explanations occur. Either that there is an allosteric interaction at the receptor site or that carbenoxolone increases the synthesis of, or inhibits the destruction of, an aldosterone-induced protein which indirectly improves the efficiency of the sodium pump.

That carbenoxolone may also exert effects at renal level is suggested by two studies. When salt intake is restricted to 26 m-equiv/day in patients receiving 300 mg of carbenoxolone daily, no retention of Na, water, or chloride occurs while simultaneously, aldosterone secretion falls to a third of control values.\footnote{50} Plasma renin levels seemed unaffected but when 10 patients with bilateral...
adrenalectomy for the control of Cushing’s disease were given 100 mg carbenoxolone daily for 10 days, plasma renin fell significantly, blood pressure rose from below normal to normal, serum sodium rose and potassium fell significantly suggesting that carbenoxolone does, in fact, exert some action upon the nephron.61 This has been suggested by previous studies in the rat and the dog.62 In general, carbenoxolone has antidiuretic effects which are dose-related but the evidence in animals that the amount of sodium in the tubules influences the excretion of potassium is supported by human studies.45 In three of 10 patients given up to 300 mg of carbenoxolone sodium daily, after a 50 g oral glucose load, three showed definite impairment to glucose tolerance and all had low levels of plasma potassium.63 Liquorice and its derivatives have little or no glucocorticoid activity64, and, whereas the administration of corticosteroids produces an increase in fasting and post-glucose insulin levels,65 in these patients the insulin response to glucose was impaired. A similar impairment of carbohydrate tolerance has been observed when patients treated with thiazide diuretics develop hypokalaemia.

The pharmacological properties of drugs are greatly influenced by the degree of protein binding. The blood concentration of carbenoxolone and its metabolites represent up to 80% of administered doses.66 At therapeutic levels in the plasma (10-100 μg/ml) the drug is more than 99% bound to plasma protein in a number of species including man. Albumin binds with 83% and globulin with the remainder. Two different classes of binding sites on albumin have been identified.67 It is this binding character which probably accounts for the rarity of toxicity as without this its capacity for uncoupling of oxidative phosphorylation would prevent its use in man. In the study by Downer and his colleagues it was shown that orally administered carbenoxolone does not appear in the plasma when an alkaline mixture is simultaneously used to buffer gastric acid secretion but does so when the intragastric pH returns to less than 2. After introduction to an empty stomach the maximal plasma level of the drug is reached in one hour, but another peak appears at four hours, presumably related to the enterohepatic circulation of bile. Seventy to 80% of a dose of 14C-carbenoxolone is excreted in the faeces and 1% or less in the urine.68 The faecal component is probably carbenoxolone-30-glucuronide and is hydrolysed by the gut flora to B-glycyrrhetic acid. Studies in different species, including a group of rats in which sterilization of the gut was obtained with antibiotics to prevent bacterial hydrolysis in the stomach, show that it is the carbenoxolone, and not its hydrolysis product B, glycyrrhetic acid, which is the active healing agent. The evidence that in rats, whose stomachs, because of coprophagia, invariably have an active microflora, pretreatment with antibiotics changes the pattern of the metabolism to that found in the squirrel, monkey, and man69 provides a possible explanation of the relative failure of the drug to heal gastric ulcers in rats. In man it appears that carbenoxolone is transported through the gastric mucosa, becomes bound to plasma proteins, is conjugated with glucuronic acid and excreted in the bile. It does not undergo hydroxylation or reduction because the protein-binding prevents it from entering the phospholipid envelope of microsomal cytochrome P-450 and exposure to enzyme attack.

Single case reports of hypokalaemic myopathy and myoglobinuria and hypokalaemic nephropathy have appeared.60,61 The reasons for the side effects are as yet undetermined. Their appearance in any one individual treated with carbenoxolone sodium is unpredictable and has no relationship
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to dosage. The author recently had a patient who had been given a daily dose of 200 mg of carbenoxolone sodium for 18 months and she had neither oedema nor hypertension nor hypokalaemia.

The chance of patients suffering any of the reported side effects of water retention, hypertension, hypokalaemia, myoglobinuria, and myasthenia is difficult to assess. From data on drug sales provided by the manufacturers and by the Committee for Safety in Medicine, approximately 160 000 patients received the drug in the past two years, yet only in 19 instances were adverse effects reported to the Committee. The majority had oedema only, seven had hypokalaemia, two myoglobinuria, and there were three with myasthenia. This is probably an underestimate of the total experience as doctors do not readily subscribe to voluntary reporting, and in a recent report of a trial of a carbenoxolone analogue (BX24) 46% of the patients with gastric ulcer who were given 300 mg of carbenoxolone daily for four weeks, for comparison purposes, developed fluid retention and electrolyte disturbance. \(^2\) During this period of two years no deaths attributable with certainty to carbenoxolone have been reported.

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References

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