

CREON

Integrating the patient experience into clinical practice

Mark Buckley-Sharp MBBS DipBiochem FRCPath

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What is Creon?

- A prescription only medicine (POM).
- Extract of digestive enzymes from pig pancreas; pelleted, and with each pellet having a soluble (acid-resistant) coating; packaged in gelatin capsules.
- Two available 'strengths' contain Lipase - 10KU and 25KU.
- Other main enzymes are Amylase and Protease, at relative unit strengths of 64% and 4% of Lipase respectively.
- Other pancreatic enzymes are present, but are not standardised.
- Shelf-life is three years from manufacture.
- Enzymes degrade during storage, therefore KU activity of capsules reduces.

Indications for Creon

- Pancreatic insufficiency requiring digestive enzyme replacement. The indications are for mal-digestion. Whilst mal-digestion prevents proper absorption by the gut, the primary disorder requiring Creon is not a mal-absorption.
 - Congenital
 - Cystic fibrosis (majority users of Creon)
 - Acquired
 - Chronic pancreatitis
 - Surgical pancreatectomy

Symptoms of Mal-Digestion

- Traditionally:
 - The production of copious and foul-smelling stools, which are hard to flush away. The latter being caused by dietary fat remaining in the stools.
- More comprehensively:
 - Upper-gut bacterial overgrowth, leading to fermentation of poorly digested food, and excessive wind.
 - Feeling of fullness, and cramping pains due to excessive volume in the small bowel.
 - Extreme lethargy (24h). ? Due to fluid shifts. Also called 'late dumping'.
 - Osmotic purge due to large amounts of undigested food in the large bowel.
 - Excessive flatus due to large bowel bacteria being 'overfed'.
 - Deteriorating nutritional status due to lack of available digested food.
 - Macronutrients: Energy, Protein
 - Micronutrients: Vitamins, Minerals

Effects of Creon

- Creon restores (reasonably) adequate digestion, thus also removing the effects of mal-absorption

Prescribing & Dispensing Creon (Primary Care and TTAs)

- Rx (Recipe):
 - **Always prescribe both strengths of Creon so that the patient can make up any required dose.**
- M (Mitte):
 - **Always prescribe in multiples of the pack size.**
 - The pharmacist should never be required (and should query any request) to open a pack to dispense it in part. Once opened, the material will deteriorate more quickly, and the use-by date on the pack is invalidated.
 - The standard pack sizes are currently 100 capsules for both 10KU and 25KU strengths. A pharmacist can advise if availability changes.
 - Always overprescribe packs. Do not attempt to calculate an exact number for the standard 28 day prescribing period.
 - Agree with the patient:
 - The patient will maintain an adequate forward stock to protect against any supply interruption.
 - The patient will arrange with the community pharmacist to under-dispense against the prescription as required to manage the personal stock.
- Dosage:
 - **Dosage must always be 'As Directed'**
 - The prescription must not state an actual dose of capsules, or timing.

Prescribing & Dispensing Creon (Inpatients)

- **Creon prescriptions must be 'prn' without stating the dose.**
- Creon is not a controlled drug and does not need to be kept locked away.
 - For patients already taking Creon:
 - Always prescribe their current strengths of capsules on the chart.
 - Ideally, have the patient use their personal stock and let them keep it for immediate access. Dispense whole packs to top up as required.
 - For patients newly starting Creon:
 - Always prescribe both 10KU and 25KU capsules on the chart.
 - Patients will need advice and assistance with dose calculation from a dietician or other adequately informed clinician.
 - Use discretion, and agree with ward pharmacist, whether to dispense whole packs to the patient, or whether to dispense individual capsules prn from ward stock.
- **Creon must be dispensed so that it is available to be taken exactly with all food. It cannot wait for routine drug rounds.**

Effect of Anatomy on Digestion

- In the normal state, the stomach holds food for acid maceration; for the start of protein digestion; and for a degree of sterilization.
- Where the pylorus is excised (gastro-jejunostomy; traditional Whipple's), food will pass to the jejunum before complete maceration. This will:
 - Mechanically limit digestion.
- Where the pancreas is connected to the stomach (Whipple's variant), the patient will be on acid suppression with Omeprazole. This will:
 - Limit maceration and sterilisation.
 - Make upper gut colonisation more likely.
 - Increase the risk of cholangitis and/or bacterial gastroenteritis (food poisoning).

Assessing the Acute Need to Start Creon

(Omitting congenital cystic fibrosis and gradual deterioration in chronic pancreatitis.)

- After total pancreatectomy, Creon can be assumed to be required. After partial pancreatectomy, patients should be formally assessed when starting food.
- Document clinical history about:
 - Diarrhoea or urgency.
 - Passage of apparently unchanged food.
 - Short transit time of unchanged or poorly digested food.
 - NOTE: Opioid pain relief may inhibit gut motility.
- High calorie supplements, such as Ensure, should not be offered unless a pancreatic defect has been ruled out, or Creon support has been started.
 - Ensure, etc., can have a dramatic and unpleasant effect with pancreatic insufficiency.

Starting a Patient on Creon

- **A dietician, a clinical nurse specialist, another informed clinician, or some combination of these, must provide direct and effective patient education.**
- Provide a copy of any locally available patient handbook.
- The educating clinician(s) should explain about:
 - The purpose and general usage of Creon.
 - Compositions of foods and how these affect Creon dose calculations.
 - Problematic foods.
 - A starting level of dosage, and how this is calculated.
- The educating clinician(s) should also explain to the patient that:
 - Finding a workable pattern of foods and Creon doses takes experience.
 - There will be mistakes and problems from which to learn.
 - The patient will eventually know more about their own Creon usage than any clinician.
- **The patient will meet many clinicians who know nothing useful about Creon. It will then be the patient's turn to educate.**

Cultural Issues with Creon

- The materials present in Creon may cause difficulty with certain cultural groups:
 - Vegans may object to the animal sources of the materials.
 - Hindu patients may object to the bovine source of the capsules.
 - Jewish and Muslim patients may object to the porcine source of enzymes.
 - Contradictory opinions range from prohibition to acceptability on grounds of necessity.

How to Take Creon

- Creon capsules should be swallowed whole, and taken at the same time as food.
- An alternative is to open the capsule(s) and sprinkle on food. This must only be done with food which will not be chewed, such as soup or puree.
- Where the food amount requires multiple capsules, then the dose should be divided during the whole meal.
- Food and Creon should be taken with a good quantity of fluid. Do not underestimate the quantity of fluid provided by the stomach, bile and pancreatic juice in the normal person, where these quantities may not be secreted in an affected patient.

Very Important for Patients

- **Always carry Creon. Stock up with a whole day's requirements each morning, of whatever mix of capsules is typically needed, plus spares.**

Adverse Effects of Creon

- Adverse effects are listed in the manufacturer's advice leaflet. Some of these are realistic, but some are improbable and appear to be just for regulatory cover.
- Allergy:
 - Rare but always possible with any medicine on first exposure.
 - Allergy may be to the pig pancreatic extract, or the beef gelatin capsule, or to other components.
 - Allergy may show as a skin eruption. However, as none of the medicine is absorbed, it may only show as gut cramps (an 'internal' eruption?)
- Long-term and in very high doses:
 - Large bowel strictures are reported as a late reaction to the excipients.
- Reported adverse effects which are improbably related to Creon:
 - Diarrhoea / Constipation.
 - Creon contains no more than a trivial amount of protein: less than a small spoonful of boiled egg. Like normal pancreatic enzymes, it is itself digested on passage through the gut.
 - Taking too little Creon is a more likely cause of diarrhoea.
 - Taking more Creon, and moving from a state of purge to normality, might be wrongly interpreted as constipation.
- Adverse effects not mentioned, but which should be considered:
 - If Creon capsules are opened and chewed with food, then Creon pellets may get lodged between the teeth. The pellet is then likely to activate and digest the gums.
 - Excessive Creon may persist in the gut and cause anal irritation.

Calculating Creon Dosage - Introduction

Overall, there are some very dubious recommendations available on the internet.

A) Suggestions from various sources which should be ignored:

- “500-2500U per kg body weight per meal.”
 - This is widely quoted, including by US-FDA, but is a bizarre suggestion. Creon is not absorbed. Body weight cannot be related to any volume of distribution and the wide 5:1 range is too vague to be helpful.
- “The patient should only change the dose on medical recommendation.”
 - On the contrary, the patient must be in charge of calculating the dose, within clinical advice, depending on the food eaten.
 - The patient does need education about the method of calculation.
- “Dose adjustments should be made over several days.”
 - No. Unless this refers to changing the method of calculation to find a better optimum dosing schedule. Even then there is no need to delay a change.

B) Rather more sensible suggestions, including from the manufacturer and from Pancreatic Cancer UK:

- “25-50KU per meal”
- “10-25KU per snack”
- “Try 10KU per 6g fat”

C) Other available suggestions worth considering:

- “Up to 4KU per 1g fat”
- “A patient taking more than 10KU per kg body weight per day should be carefully reviewed:”
 - This level (say >500KU/day) has the potential for long-term toxicity.
 - The patient may be taking far too much more than actually required.
 - For some reason, such as timing, the medication may be ineffective.

Calculating Creon Dosage Pragmatically

These suggestions are based on personal experience with some extrapolation.

The recommended doses are all much less than that produced in the normal physiological state, so taking a bit more than suggested should never be a problem.

Food and eating patterns:

- Try to settle into a predictable pattern of eating, not necessarily by time but by types and amounts of food.
- A predictable pattern of foods should give a predictable pattern of doses.
- Take Creon at the start of any meal. If multiple capsules are used, space them out during the meal.
- At a restaurant, where courses may be spaced out, treat each course as a separate meal with its own dose plan.
- Learn about the labelling of foods in supermarkets, especially fat content.
- From that, learn to estimate the content of fresh foods, unlabelled foods, or anything you may be offered to eat.
- Oils and fats used in cooking must be included in your calculations, as must the basic energy staples of potatoes, rice, maize, and cereals. But, sugary confections and drinks, fruit, and other vegetables can be ignored.
- If you believe you have at least some pancreatic function, then try taking no Creon with small snacks like one biscuit or the milk in tea/coffee.

- Learn to recognise foods which are highly imbalanced. Manage their use since they can put you over your estimated normal range(s) of content.
 - Cheese and pastry are about 50% fat.
 - A fondue could be disastrous!
 - Indian cuisine has much more fat than Chinese cuisine.
 - An egg is about 30g protein.
 - Pasta is high in carbohydrate.
 - Beware high energy food supplements. Ignore advice to use them.
- Don't overeat just because you are enjoying yourself.

Dose based on food:

- **When beginning to use Creon, try a starting dose of at least 1KU per 1g fat.**
 - A reasonable daily diet includes at least 70g fat.
 - Since the medicine is reducing in strength on storage, slightly overestimate the dose numerically. There is no need to be exact. Round doses up to the next capsule amount (10 or 25KU).
- In summary, aim to start at a minimum of 100KU per day, divided between meals roughly in proportion to size.
- Then, experiment until you can settle into a simple plan which is easy to remember.

For the Experienced User

- If the dose schedule works, then you are taking either enough, or possibly more than necessary.
- It takes some planning and courage to break a pattern that works.
- I have managed my doses with relatively few problematic incidents for over 10 years. However, it took over 6 months to find this working pattern.

Supplement 1

LONG TERM MANAGEMENT OF MICRONUTRIENTS AFTER WHIPPLE'S PROCEDURE

Macronutrients (Fat, Protein, Carbohydrate and Total Energy) are adequately managed after Whipple's procedure if the patient can maintain a stable body weight. This note concerns the long term management of micronutrients where deficiencies may be occult and insidious in onset.

There should be planned surveillance for micronutrient deficiencies by agreement either by surgeons during follow-up, or by the primary care physician. (Consider adopting the advice offered for use after bariatric surgery.)

Fat Soluble Vitamins

- Relevant vitamins include A, D, E, and K.
- Of these, vitamin D may be the easiest to use as a proxy marker. Measurement of Serum Vitamin D is feasible but very expensive. Taking a vitamin D supplement is easy and much cheaper.
- The risk of vitamin D deficiency arises from possible malabsorption of the vitamin, consequent on maldigestion of fat.
- Maldigestion of fat should be treated with Creon replacement, but vitamin D deficiency should always be considered.
- It may be convenient for the patient anyway to take a continuous OTC multivitamin supplement, which provides 100% of recommended daily amount (RDA, 5ug) on top of the normal diet.
- Any vitamin D deficiency detected while on OTC supplementation may require review of other fat soluble vitamins and consider using a higher dose of supplement.

Water Soluble Vitamins

- Relevant vitamins include B-series, Folate, and C.
- Of these Vitamin B12 is the only likely problem, where the risk arises if partial gastrectomy has diminished intrinsic factor. Measure Serum Vitamin B12+Folate, and review against any FBC results (? macrocytosis).
- The normal liver store of vitamin B12 is up to 2 years. A deficiency is unlikely to be detected sooner than this after Whipple's procedure.
- As with fat soluble vitamins, use of a continuous OTC multivitamin supplement may be convenient. However, this will not contain intrinsic factor.
- Any vitamin B12 deficiency detected while on OTC supplementation may require replacement by injection.

Minerals

- **It is not widely realised that the only site of active iron absorption is in the duodenum.** This is removed by Whipple's procedure leaving only a highly inefficient passive absorption process in the small gut.
- While gross iron deficiency leads to measurable anaemia, slow onset iron deficiency leads first to low ferritin without anaemia. Measure Serum Ferritin rather than FBC.
- It may be desirable for the patient anyway to take a continuous OTC multivitamin supplement also containing 100% RDA of minerals including iron.
- Any low ferritin detected may require review of other minerals and prescription of pharmacological doses of iron. As the patient will be unable to absorb iron quickly, what is required is a tolerable dose of iron which can be taken long term. Consider Ferrous Sulphate, 1 daily, and continue to review Serum Ferritin.
- Other minerals of interest may include copper, zinc and selenium. Serum levels of these can be tested if required.

Supplement 2

PERI-OPERATIVE FLUIDS

Introduction:

- The “British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients” were published in 2011 by a group of six professional bodies including those for Surgery, Intensive Care, Nutrition and Clinical Biochemistry.
- The principal concern was that intravenous fluids can be given without adequate policies or planning, leading frequently to incorrect use.
- Of necessity, the following are highly abbreviated and the full guidelines should be studied in order to review current practice and identify improvements.

Headlines:

- The only routine iv crystalloid solution used should be Hartmans (or Ringer).
- All patients require adequate amounts of free water per day as iv 5% Dextrose.
- Any patient who develops interstitial oedema has been overdosed on electrolyte. or water, or both, although capillary leakage of albumin may be a factor.
 - Oedema compromises tissue viability. While some oedema at the operative site is inevitable, peripheral oedema is not.
- **Routine use of 3 L IV of saline per day is never an acceptable treatment.**

Principles:

- There are only three purposes for intravenous fluids. Prescriptions of fluids should be capable of explicit justification against each of these separately and in combination:
 - Replacement of normal baseline requirements.
 - Replacement of identified or estimated losses.
 - Resuscitation.
- The following give more detail, but are not relevant for children or for those with renal failure where quantities must be much more carefully considered.

Normal Baseline (24h) Requirements:

- 1.5 – 2.5 L of volume
 - For respiration, sweating, and a realistic urine output.
- 70 mmol Sodium
 - The guidelines show a range, but 70 is easy to remember as 0.5 L of isotonic crystalloid solution (Hartman’s, not Saline).
 - Many drugs eg, antibiotics contain significant amounts of sodium, and this should be considered in any calculations.
- 70 mmol Potassium
 - The guidelines show a range, but 70 is easy to remember, being the same as sodium.
- The simplest baseline replacement is 1.5-2.0 L 5% dextrose and 0.5 L Hartmans per day, with potassium added during the regime.

Replacement of Losses:

- Urine is covered by the baseline requirements and is not a loss to be replaced.
- All drains, including gastric drainage, should be replaced mL for mL with crystalloid added to the baseline.
- Invisible internal losses into the gut may have to be estimated but are temporary.

Measurements:

- Serum U&E are traditional, but are uninformative unless severely disordered.
- Consider Urine electrolytes (Na,K) as a far better indication of imbalances.
- Review urine volume and apparent concentration.