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TABU

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Summary

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Indispensable co-operation – transparent rules of the game needed

The esteemed British Medical Journal (BMJ) devoted a substantial amount of column space last May [1] to ponder upon the relations between physicians, researchers and the pharmaceutical industry. Amongst others, a meta-analysis of the publication of results of medical research sponsored by the pharmaceutical industry.[2]

The involution of the pharmaceutical industry and physicians is a global phenomenon. The truth of the matter is that all the medicines developed over the last 60 years have been developed and produced specifically by the pharmaceutical industry. It is just as obvious that the research and development of medicines would not have been possible, nor is it now, without the co-operation of medical experts, whether they are research scientists or clinical practitioners.

The co-operation and involvement becomes problematic, when the pharmaceutical industry's research, public relations (with, patient organisations, amongst others), sales promotion, dissemination of information, or marketing, has undesirable effects on the community. Examples of this include undermining the public's confidence in the independence of medical prescribing, distorting the results of medical research and their publication, and the practices censured by the society, including the giving, requesting and accepting of benefits and gifts.

A particularly disconcerting finding of the above-mentioned analysis is, that research funded by the pharmaceutical industry more often than not leads to results favouring the medicines of the sponsoring manufacturer, as opposed to research funded from other sources. This could not be explained away by the quality of the research. It was surmised that the phenomenon was based on the selection of inappropriate comparator products or dosages thereof, and publication bias.

It is estimated that there are about 80 000 company representatives in the United States of America, whose activities were funded to the tune of 19 billion dollars by the pharmaceutical industry's sales promotion funds in the year 2001 alone.[3] In Finland, this phenomenon exists on a totally different scale. Nonetheless, here we have had to clarify the borderline between the forbidden and the acceptable in various contexts in cases related to sponsored travel for physicians, or goods supplied gratuitously to them.[4]

Legislation, supervision by the authorities, and self-regulation by various parties have been tightened, and the same can also be done in the future. More importantly, a code of conduct suitable for the Finnish community and applicable to the whole pharmaceutical field needs to be developed to cover the various kinds of dealing and transacting, whereby transparency would be emphasised. The number of problem situations would be reduced if transparency in co-operation, including the funding of projects, were increased.

1 BMJ Volume 326, 31 May 2003.

2 Lexchin J, Bero LA, Djulbegovic B, Clark O: Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 326: 1167-1170, 2003.

3 United States General Accounting Office. Prescription drugs: FDA oversight of direct-to-consumer advertising has limitations. GAO-03-177. October 2002. www.gao.gov/

4 National Board of Medicine 24.6.1985, Record no. 6508/03/82; National Board of Medicine 5.2.2001, Record no. 1261/63/2000; Parliamentary Ombudsman 30.12.2002, Record no. 1082/2/99.

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Summary

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Treatment of constipation

Constipation occurs in 2–20% of the population. It is most common in women and its occurrence increases with age. The complications consist of hard stool, decreased frequency of elimination and occasionally difficult evacuation of the faeces. According to the most commonly used criteria, the defining characteristics of constipation are: a frequency of elimination less than 3 times a week, hard stool, often straining at stool, the symptoms occurring during at least 12 weeks in one year. International (1) survey have been published recently on the diagnosis and treatment of constipation.

The related factors may be associated with lifestyle and diet, structural causes, certain medications, and endocrine, metabolic and neurological diseases (Table 1). Onset or exacerbation of discomfort caused by constipation associated with the introduction of a new drug is a good indication of a history of a disease. Exclusion of any organic causes is recommended, especially if the symptoms are new or if they are associated with melaena, anaemia or with weight loss. However, usually no definite organic cause is found and the symptoms may be considered functional.

Different types of constipation

Functional constipation can be classified according to the symptoms and findings as follows, slow intestinal transit, pelvic floor functional disturbance (outlet obstruction, paradoxical puborectalis syndrome, anismus) or irritable bowel syndrome (1, 2, 3, 4). In practice, the classification is useful even though the symptoms in many patients include features of several types of constipation. Patient history and clinical examination combined with sigmoidoscopy and laboratory tests such as haemoglobin, fasting blood sugar, thyroid stimulating hormone, blood creatinine, and blood calcium are usually adequate. Examination of the transit time and defaecography are occasionally necessary, but anal manometry and neurophysiological examinations of the anal area are very seldom required.

The frequency of bowel movements in patients with constipation of the functional slow transit type is once a week or less. The stool is too hard, the response to conventional treatment is poor and gradually the urge to defaecate decreases. Prolonged intestinal transit time can be established by a transit time examination which consists of the patient swallowing small X-ray positive pieces of plastic which remain undigested in the digestive tract. In the atonic large intestine (colonic inertia) the pieces remain in the ascending colon or in the neighbourhood of the colon, whereas in outlet obstruction due to pelvic floor muscular dysfunction they remain in the sigmoid colon and in the rectum.

Patients with constipation characterised by pelvic floor dysfunction have difficulties with the evacuation of the faeces, they frequently need to strain at stool, faecal impaction occurs in the rectum and the frequency of elimination may be normal, or higher or lower than normal. The intestinal transit time is normal or slightly prolonged. In examining such cases, defaecography (contrast study), anorectal manometry or electromyography (EMG) may be used. Defaecography can detect whether the patient's anal sphincter, and especially the puborectal muscle, is not relaxing in the normal way during defaecation. Similarly, manometry and EMG can detect paradoxical constriction of the anal sphincter during defaecation. The studies are situation-sensitive and the results are not particularly specific. Any cases of rectocele, enterocele or prolapse of the rectal mucosa will also be detected by defaecography.

Constipation is the dominant symptom in some patients suffering from irritable bowel syndrome. The symptoms typically include abdominal pain and swelling, difficulty in evacuating the bowel, inspissated and pelleted stools and occasional bouts of small-volume diarrhoea.

Treatment of constipation

Proper guidelines for a lifestyle and a correct diet are the basis of treatment (Table 2). The guidelines for a lifestyle should consist of a review of and training in the habits and event of evacuation. It would be beneficial to include intake of additional fibre and increased consump-

Table 1. General causes of constipation

Life-style
- *Insufficient consumption of fibres*
- *Insufficient consumption of water*
- *Lack of exercise*
- *Unnecessary inhibition of the defaecation reflex*

Medication
- *Calcium-channel blockers*
- *Diuretics*
- *Neuroleptics*
- *Antidepressants*
- *Iron supplements*
- *Statins*
- *Anti-inflammatory analgesics*
- *Opioids*
- *Anticholinergic agents*
- *Antacids*

Metabolic and endocrine causes
- *Hypothyroidism*
- *Diabetes*
- *Dehydration*
- *Hypercalcaemia*
- *Hyperkalaemia*
- *Uraemia*

Neurological causes
- *Palsy of CNS origin*
- *Spinal cord injuries*
- *Multiple sclerosis*
- *Parkinson's disease*

Causes related to the intestine
- *Structural causes*
  - *intestinal obstructions: neoplasms, strictures of varying etiology, diseases of the anal area*
- *Functional causes*
  - *spastic pelvic floor syndrome (outlet obstruction), slow intestinal transit,*
- *Irritable bowel syndrome*

tion of water in the dietary advice. In addition to fibre, medicinal fibre (bulk laxatives) may be used. Fibre increases the faecal mass and accelerates the intestinal transit time. Our normal nutrition usually contains 15–20 grams of fibre per day, whereas the recommended amount is 25–35 grams per day. Additional fibre is obtained by increasing the consumption of greens, root vegetables, fruit, wholemeal products and bran, or the daily use of 10–20 grams of fibre preparations available from the pharmacy. This treatment is usually adequate for patients with constipation associated with irritable bowel syndrome and even for patients with functional outlet obstruction. The increase of fibre in the diet causes flatulence in many people and, as a result, an adequate amount of fibre is often not achieved in the diet. For patients with severe constipation of the slow transit type, additional fibre in the diet is not usually an adequate measure.

Mainly osmotically active laxatives such as lactulose, lactitol, milk of magnesia and polyethylene glycol (macrogol) would be appropriate for use when additional fibre intake alone is not sufficient. Lactulose and lactitol are disaccharides which are not degraded in the intestine until after the effect of bacteria in the large intestine; they reduce the intestinal pH and accumulate liquid in the large intestine. Fast-acting lactulose and lactitol appropriately complement the laxative effect of fibres. Lactulose and lactitol also cause flatulence, which restricts their use, and their efficacy is often not enough for patients with severe constipation. Milk of magnesia does not generally cause flatulence and is appropriate for use especially in addition to fibre treatment. There is a risk of hypermagnaesemia in patients with renal failure.

Macrogol is an osmotic laxative with insignificant absorption from the intestine (5). For nearly 20 years it has been used as a substance promoting evacuation of the large intestine in preparation for a coloscopy. In recent years, it has also been introduced in the treatment of chronic constipation (5). The substance is effective and clinical studies have also found it safe to use (6). Macrogol is especially recommended for use in patients with severe slow transit constipation. Adverse reactions may nevertheless include flatulence, nausea, excessive diarrhoea and associated dryness and faecal incontinence. Unfortunately, the drug is rather costly and is not refundable by health insurance in Finland.

Laxatives with intestinal stimulation include senna, bisacodyl and sodium picosulphate preparations. In previous studies, they have been suspected of having caused damage to the intestinal nerves (7) and being capable of causing intestinal sluggishness with long-term use. In later studies, it has not been possible to obtain definite confirmation of this (8), but caution is still exercised in the long-term use of stimulating laxatives. When they are used, the intestinal evacuation may be powerful and even painful. Sodium picosulphate is used by practical oral administration in the form of drops allowing individual dose adjustment. In the severe slow transit type of constipation, macrogol, if necessary together with a stimulating laxative is often the most effective treatment.

Prokinetic cisapride accelerates the large intestinal transit time and relieves the constipation (9). Cisapride may nevertheless also cause painful spasms. It has subsequently been found to have complex interactions with certain drugs and its use is no longer recommended. In Finland at present, there are no prokinetic drugs in use which would effectively increase the large intestine motility. A new 5-hydroxytryptamine (5-HT_4) receptor agonist, tegaserod has been found to be especially beneficial in the treatment of patients with irritable bowel syndrome of the constipation type.

Table 2. Treatment of constipation

Mild constipation
- *increased intake of fibre*
- *an extra 2 glasses of water after every meal*
- *use of bulk laxatives and/or lactulose or lactitol*

Irritable bowel syndrome and constipation
- *use of a bulk laxative and dietary advice*

Pelvic floor dysfunction syndrome
- *training in defaecation physiology*
- *use of a bulk laxative*
- *biofeedback treatment*

Severe slow transit constipation
- *macrogol and stimulating laxatives when needed*
- *biofeedback treatment*
- *surgery*

Biofeedback treatment is aimed at relaxing the pelvic floor muscles and restoring their normal function in association with defaecation. The treatment has been found to be of benefit especially to patients suffering from pelvic floor dysfunction (10), even though the symptoms tend to recur gradually after discontinuation of treatment (11). Treatment is given by physiotherapists familiar with this type of treatment. This is recommended in patients well motivated towards treatment, but following a review of the defaecation event and associated medical therapy the results appear inadequate.

Surgical treatment, usually colectomy and ileorectal anastomosis, may be considered in patients with constipation of the slow transit type with inadequate response to other treatment.

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Summary

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Gastrointestinal adverse drug reactions in Finland in 1973–2003

Various gastrointestinal complaints are among the commonest of the medical symptoms. For example, an estimated 20-40% of the population complains from time to time of upper abdominal discomfort. Abdominal complaints in the population are common, and distinguishing adverse drug reactions (ADRs) from abdominal dysfunction such as nausea, indigestion, constipation and diarrhoea may consequently be difficult, if not impossible, in practice. Due to the high incidence of gastrointestinal symptoms, under-reporting of the symptoms may occur, especially when the reaction is not unexpectedly intense or severe. However, if there is a known explicit or suspected mechanism which gives rise to the suspicion that the effect is, in fact, that of a medicinal substance, it becomes considerably easier to assume or actually to indicate and report the causal relationship. The number of alimentary tract related adverse reactions reported to the National Agency for Medicines between 1973 and end of June 2003 was about 2 000, which is approximately 10 % of all ADRs reported in the country.

This is a summing-up of the most common adverse reactions, the mechanisms of which are known, either in part of fully, and the implications of which are the most serious ones even for the patient. These are the criteria by which the adverse reactions reported have mainly been defined, as various cases of gastrointestinal bleeding, lesions and drug-induced infections or exacerbations of them. In general, the alimentary-tract-related adverse reactions are, by percentage, spread over the various drug groups similarly to the description given in the survey published in the issue 3/2003 of the journal TABU. The most common salient exceptions occur in the case of antimicrobials (34% vs. 28%) and preparations used for the treatment of diseases of the musculoskeletal system (18% vs. 11%), the gastrointestinal adverse reactions of which are more numerous than the relative amount of all ADR reports related to these drug groups (Table).

The number of cases of suspected drug-induced gastrointestinal bleeding was 240 over a period of 30 years. The number includes cases of haematemesis as well as bloody diarrhoea. Furthermore, a total of 20 cases of bleeding ulcers, perforated peptic ulcers and internal abdominal bleeding have been reported. In 21 cases bleeding was fatal. The overwhelming majority of cases of bleeding has been reported in association with the use of broad spectrum penicillins, i.e. amoxicillin and other ampicillin derivatives (28% of the total), but just the number of reports associated with the use of phenoxymethylpenicillin make up 20% of the total, i.e. nearly half of the reported cases are associated with penicillin derivatives. The most com-

Gastrointestinal adverse reactions reported to the ADR register during 1973–2003, divided by drug groups

	percentage of reports, %
Anti-infectives for systemic use	*34*
Musculo-skeletal system	*18*
Cardiovascular system	*14*
Nervous system	*14*
Alimentary tract and metabolism	*5*
Genito-urinary system and sex hormones	*4*
Respiratory system	*3*
Blood and blood forming organs	*2*
Antineoplastic and immunomodulating agents	*2*
Radiopharmaceuticals	*2*
Dermatologicals	*1*
Hormonal preparations (excl. sex hormones)	*1*
Antiparasitic products, insecticides and repellents	*1*

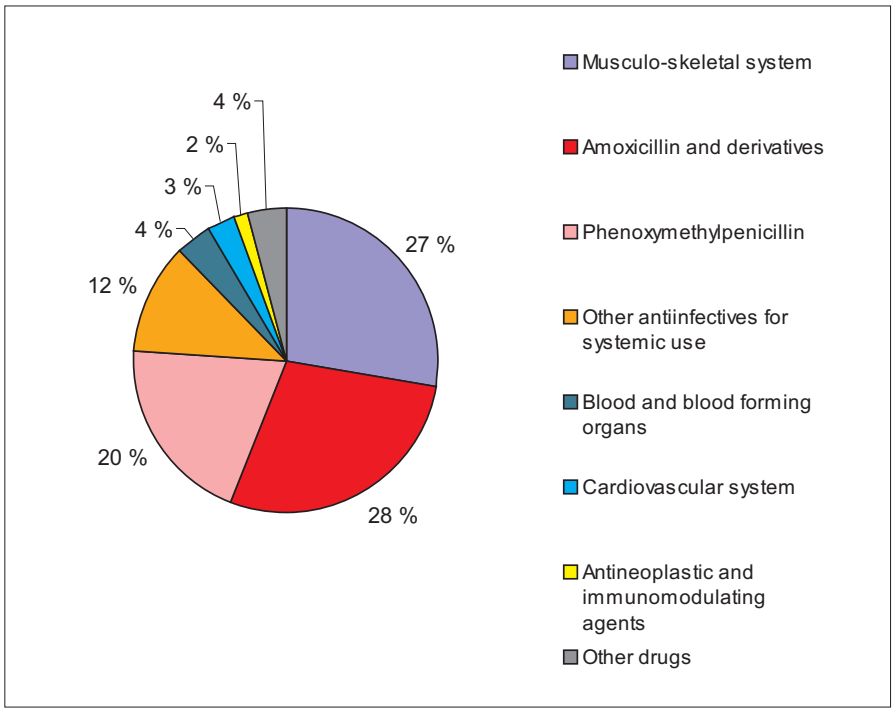
monly used term of all has been melaena, and only 38 reports refer specifically to *Clostridium difficile* infection, pseudomembranous colitis or haemorrhagic colitis. It is presumed nevertheless that the cause in the majority of cases associated with the use of ambicillin derivatives and cefalosporins has been pseudomembranous colitis associated with *Clostridium difficile*. It is interesting to notice, indeed, that cephalosporins, and cefuroxime axetil in particular, were the most important cause of *Clostridium difficile*-induced diarrhoea reported in the material compiled during the 1990's from the hospitals of Helsinki.

Inhibition of prostaglandin synthesis associated with the mechanism of action of anti-inflammatory analgesics and, in particular, the reduction induced by anti-inflammatory analgesics in the synthesis of prostaglandin E_2, which protects the abdominal mucous membrane, is a characteristic predisposing factor for peptic ulceration, perforated peptic ulcers and gastrointestinal bleeding. Indeed, about a third of the reported cases of gastrointestinal bleeding, ulcerations and perforations have been associated with the continuous use of high doses NSAIDs.

Antimicrobials and NSAIDs were suspected to cause over 75 % of GI bleedings reported to NAM (Fig). Strangely enough, heparin derivatives and warfarin, which merely by their mechanism of action are factors predisposing to bleeding, have only been the subject of 12 reports associated with gastrointestinal bleeding. Equally, there are only 4 reports on anti-cancer drugs which, by their mechanism of action, predispose the patient to mucous membrane damage.

The most common adverse reactions reported at the end of the 1970's and beginning of the 1980's were oesophageal corrosion and inflammation, nearly 100 cases of which were reported to have been associated especially with the use of both tetracycline and doxycycline. During the same period, about 40 reports were received regarding the oesophageal damage caused by an anticholinergic agent, emepronium, used to abate the increased need for micturition and improve urinary retention. The cases were most commonly associated with the intake of the drug with inadequate amounts of liquid. Following the identification of the adverse reaction and the associated cause, the reporting of the reactions ceased in practice in the mid-1980's.

Reported GI adverse drug reactions in Finland 1973–2003



Ten cases of bleeding or oesophageal ulceration associated with the use of drugs for the treatment of cardiovascular diseases have been reported. The relatively high percentage (14%) of reports within this group of medicinal substances in comparison with the total number of reports is mainly explained by the general symptoms (abdominal pain, nausea, diarrhoea, vomiting) and gingival hyperplasia induced by calcium antagonists. Gastrointestinal symptoms associated with medicinal substances affecting the nervous system are often linked with nausea, vomiting and diarrhoea induced by antidepressant agents. Another well known and commonly reported adverse reaction is abdominal pain associated with the direct stimulation of the gastrointestinal motilin receptors and caused by macrolide antibiotics, i.e. erythromycin derivatives, and also nausea reported in association with the use of tetracycline.

It should be stated, by way of conclusion, that despite the wide spread occurrence of gastrointestinal symptoms in the population irrespective of whether drugs are used or not, the reports on adverse reactions related to gastrointestinal symptoms cover about a tenth of all the reports in the ADR register at the National Agency. The majority of the suspected adverse reactions have been associated with abdominal pain interpreted as functional, but among the most serious reactions, over 10% of the total number of reports were of various types of gastrointestinal bleeding associated with the use of drugs. Approximately 75% of bleeding complications were reported during the use of broad spectrum penicillins, phenoxymethylpenicillin and anti-inflammatory analgesics. Nevertheless, this should not lead us into drawing wrong conclusions when bleeding complications associated with other medications are suspected.

Translation Mervi Moisander