Soluble drug formulations: sodium content and association with cardiovascular events

An observational study has shown an association between sodium-containing formulations of effervescent, dispersible and soluble medicines and adverse cardiovascular events. While soluble dosage forms may appear convenient, it is important to be aware of the sodium content of some formulations, prescribing them with caution and only if there are compelling reasons to do so.

Overview and current advice

The Scientific Advisory Committee on Nutrition published a report on Salt and Health in 2003 which stated that increased blood pressure or hypertension was the most common outcome that has been associated with high levels of salt intake. The relationship between salt and blood pressure was previously considered in 1994 by the Committee on Medicinal Aspects of Food and Nutrition Policy. Since 1994 the evidence of an association between dietary salt intake and blood pressure has increased. The data have been consistent in various study populations and across the age range in adults.

A systematic review and meta-analysis (Aburto NJ et al. 2013) which included 36 randomised controlled trials in non-acutely ill adults, found that a reduction in sodium intake reduces resting systolic and diastolic blood pressure. The NICE guideline on the management of hypertension recommends that as part of a range of lifestyle interventions people should be encouraged to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure.

The maximum recommended salt intake for an adult in the UK is 6 grams per day; this equates to 2.4 grams (104 mmols) of sodium per day. Some medicines can contain significant amounts of sodium, including many effervescent or soluble analgesics. Certain brands of paracetamol soluble
tablets for example, can contain 19 mmols of sodium per tablet, which at the maximum daily dose of 8 tablets a day is 152 mmols per day. This exceeds the maximum recommended sodium intake for an adult for one soluble drug formulation alone, and when added to a typical Western diet this can result in a sodium intake far in excess of maximum recommended levels.

The issue of the high sodium content in certain soluble preparations particularly soluble analgesics is already known and previous initiatives have aimed to reduce their prescribing. The North West Medicines Information Centre has produced a Medicines Q+A document which lists the sodium content of a variety of indigestion preparations, effervescent or soluble analgesics, cold and flu preparations, anti-diarrhoeal preparations, cystitis preparations, laxatives, bowel cleansing solutions and other miscellaneous soluble preparations.

New evidence

A nested case-control study (George J et al. 2013) has investigated whether people taking formulations of drugs that contain sodium (dispersible, effervescent and soluble formulations) have a higher incidence of cardiovascular events compared with people taking non-sodium formulations of the same drugs\(^2\).

The study used data from the UK Clinical Practice Research Datalink (CPRD) database. The CPRD database contains data from over 500 primary care practices and covers about 7% of the UK population. All people aged 18 years and over who had received at least 2 prescriptions of sodium-containing formulations or matched standard formulations of the same drug from January 1987 to December 2010 were included in the study population. People entered the study at the date of their first prescription for a sodium-containing drug formulation or a matched standard formulation and were followed-up for a mean period of 7.23 years. The primary outcome measure was the composite of the first occurrence of non-fatal myocardial infarction, non-fatal stroke or vascular death.

During follow-up, 61,072 people had an event that met the definition of the primary cardiovascular endpoint. These 61,072 people were matched with the same number of controls from the study population (matched for age, sex and general practice). The date of the first cardiovascular event during follow-up was defined as the index date for each case and was used as the index date for the matched controls. People who had a primary cardiovascular endpoint event were more likely to have been prescribed a sodium-containing drug formulation compared with people who had not had a primary cardiovascular endpoint event (the control group); adjusted odds ratio (OR) 1.16 (95% confidence interval [CI] 1.12 to 1.21). Results were adjusted for a variety of covariates including age, sex, body mass index, smoking status, hypertension, other medical conditions including diabetes mellitus and heart failure, and co-prescribed drugs including angiotensin converting enzyme inhibitors, statins, antiplatelets and non-steroidal anti-inflammatory drugs.

When looking at the individual components of the primary outcome measure, exposure to sodium-containing drug formulations was associated with incident non-fatal stroke (adjusted OR 1.22; 95% CI 1.16 to 1.29) but it was not associated with incident non-fatal myocardial infarction (adjusted OR 0.94; 95% CI 0.88 to 1.00) or vascular death (adjusted OR 0.70; 95% CI 0.31 to 1.59). Exposure to sodium-containing drug formulations was also associated with hypertension (adjusted OR 7.18; 95% CI 6.74 to 7.65) and all-cause mortality (adjusted OR 1.28; 95% CI 1.23 to 1.33), but not with heart failure (OR 0.98, 95% CI 0.93 to 1.04). The median sodium consumption from sodium-containing drug formulations alone was 106.8 mmols per day.
The authors of the study concluded that it was the increased risk of stroke that was the main cause of the increased risk in the primary cardiovascular endpoint and that the increased risk of hypertension associated with sodium-containing drug formulations was probably the cause of the increased stroke risk. The authors acknowledge that because this study was an observational study other potential confounding factors could not be fully controlled; however the results were adjusted for a variety of covariates. In addition, data on dietary sodium intake and use of over-the-counter sodium-containing medicine formulations were not available for the study population. The authors also add that there may have been coding misclassifications for exposures, outcomes and covariates in the database.

**Commentary provided by Sue Smith, Head of Prescribing and Medicines Management, NHS Nene and NHS Corby Clinical Commissioning Groups**

In this study the median daily sodium consumption for sodium-containing drug formulations alone was higher than the maximum recommended daily sodium intake for adults. Added to a typical Western diet, these drugs could result in a very high sodium intake.

This study suggests that there are potentially significant clinical grounds for avoiding these products in almost all patients, and especially those with hypertension, those at risk of stroke or cardiovascular disease, oedema or renal failure. Clinicians should avoid prescribing sodium-containing effervescent analgesics unless there are compelling reasons to do so, such as in patients with a genuine difficulty with swallowing standard tablets or those with oesophageal stricture.

Most patients can be switched directly to a standard formulation of the same analgesic and will readily accept this change if the reason for doing so is explained to them. This advice does not apply to low-dose dispersible aspirin formulations, which contain virtually no sodium.

As long as 10 years ago, many primary care organisations promoted this message, using bottles filled with the amount of salt contained in 8 effervescent tablets as a method of demonstrating the issue to patients. The bottles of salt were used by GPs and community pharmacists in order to give a joined up message and to ensure that both prescribed and over-the-counter products were reviewed. At that time the prescribing of effervescent and soluble analgesics fell considerably as a result. This study highlights that perhaps it is worth re-visiting this simple intervention.

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References


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