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Less Use of NSAIDs in Long-Term than in Recent Chondroitin Sulphate Users in Osteoarthritis: a Pharmacy-based Observational Study in France

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Abstract – In clinical trials, long-term use of a specific chondroitin sulphate, Chondrosulf® 400 (CS400) has demonstrated symptomatic efficacy in osteoarthritis comparable to that of nonsteroidal anti-inflammatory drugs (NSAIDs) with significantly fewer side-effects. CS400 could therefore reduce the use of and risks associated with NSAIDs. A cross-sectional observational study was therefore devised in 199 randomly selected pharmacies in France to verify the concomitant use of analgesic and NSAIDs medication in patients prescribed CS400.

Consecutive patients filling a prescription for CS400 were prospectively recruited and classified into recent users (3 months or less of continuous use) and long-term users (more than 3 months of continuous use) of CS400. The main outcome measure was current and long-term use of analgesics and NSAIDs.

The 844 participating patients included 623 (73.8%) women and 221 (26.2%) men. Mean age was 65.9 years. Ninety eight (11.6%) patients did not use any analgesic or NSAIDs for osteoarthritis; 746 (88.4%) reported the use of at least one of these drugs. Compared to recent users, long-term users of CS400 had a significantly lower current (44.4 *versus* 52.5%, $p < 0.05$) and long-term use of NSAIDs (11.8% *versus* 18.5%, $p < 0.05$), and of analgesics (70.3 *versus* 79.3%, $p < 0.01$).

Mots clés :
chondroitine sulfate ;
arthrose ;
étude observationnelle ;
pharmacie ;
AINS ;
utilisation des médicaments

Résumé – Moins d'utilisation d'AINS chez les utilisateurs chroniques de chondroitine sulfate : une étude observationnelle en pharmacie. Dans les essais cliniques ayant amené sa commercialisation, une chondroitine sulfate (Chondrosulf®, CS400) a montré un effet antalgique similaire à celui des anti-inflammatoires nonstéroidiens (AINS), avec moins d'effets indésirables. Il est donc légitime de penser que son utilisation chronique en vie réelle pourrait diminuer la consommation d'AINS (anti-inflammatoires nonstéroidiens), et les risques qui leur sont associés.

De ce fait, une étude transversale a été réalisée dans 199 pharmacies choisies au hasard en France, pour évaluer la consommation concomittante d'AINS et de CS400. Des patients consécutifs venant chercher une ordonnace de CS400 ont été recrutés de façon prospective, et divisés en deux groupes : utilisateurs récents (moins de 3 mois) et utilisateurs chroniques (plus de 3 mois d'utilisation continue de CS400). La mesure principale était la consommation actuelle et chronique d'antalgiques et d'AINS.

Parmi les 844 participants, d'âge moyen 65,9 ans, 623 (73,8 %) étaient des femmes, 98 (11,6 %) n'utilisaient pas d'antalgiques ou d'AINS, 746 (88,4 %) en utilisaient au moins un. Comparé aux utilisateurs récents, les utilisateurs chroniques de CS400 étaient significativement moins fréquemment utilisateurs chroniques d'AINS (11,7 *versus* 18,5 % $p < 0,05$), mais également moins fréquemment utilisateurs courants d'AINS (44,4 *versus* 52,6 %, $p < 0,05$) ou d'antalgiques (70,3 *versus* 79,3 %, $p < 0,001$). L'utilisation chronique de CS400 s'accompagne d'une moindre utilisation d'AINS et d'antalgiques ce qui pourrait confirmer l'effet antalgique trouvé dans les essais cliniques.

1. Introduction

Osteoarthritis (OA) is a common and frequent cause of physical disability, increased healthcare utilization and impaired quality of life.[1,2] In France, symptomatic osteoarthritis concerns about 5 million persons.[3]

The pharmacologic treatment of osteoarthritis includes paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), a frequent cause of potentially serious adverse effects.[4,5] Considering that there are no long-term benefits of NSAIDs,[6] and that the gastrointestinal risk increases with duration of use, strategies have been devised to reduce risk.[7] One of these is to try to reduce the dose and duration of NSAIDs by using alternate treatments such as chondroitin sulphate.

Experimental and clinical data show that chondroitin sulphate could have an anti-inflammatory and a chondroprotective activity by modifying the structure of cartilage.[8] Because it does not act on prostaglandin synthesis, it does not share the common systemic side-effects and risks of the NSAIDs. Chondroitin sulphates have been used in various forms for osteoarthritis in Europe for more than a decade. They have recently been confirmed as first-line treatment of osteoarthritis.[9] Recent meta-analyses reviewed studies of chondroitin sulphate including published and unpublished double-blind randomized, placebo-controlled trials using a systematic quality assessment. They found moderate to large effects of chondroitin sulphate on symptoms of osteoarthritis.[10,11] As expected, the main limitations of the relevant clinical trials were the small sample sizes, the short-term follow-up and the lack of representativity of "the real life" of drug utilization. The need for studies with different designs with this drug has been widely emphasised.[12]

In a recent major clinical trial in 1258 patients with osteoarthritis, GAIT,[13] there was a significant effect of the association of glucosamine and CS in patients with an initial WOMAC pain 301-400 mm (72% responders *vs.* 54.3% for placebo, $p = 0.002$) or with celecoxib (69.4% responders, $p = 0.06$), and a non-significant effect of CS alone (61.4% responders) or glucosamine alone (65.7% responders). Another randomized double-blind study found no symptomatic effect over a year, but significant retardation of radiographic worsening in knee OA compared to placebo.[14]

Chondroitin sulphate is a complex glycosaminoglycan with polysaccharide chains composed mainly of disaccharide units. Different non sulphated and sulphated disaccharides are presents within the polysaccharide chains. Due to the presence of sulphate groups in different amounts and located in various position (4 and 6 N-acetyl-galactosamine residues), chondroitin sulphates a very heterogeneous family of polysaccharides, in terms of degree of sulfatation and molecular mass.[15] The pharmacological activity of chondroitin sulphate is dependent on the proportion of the various localizations of their sulphatation and on their molecular mass.[16] A meta-analysis confirmed that the clinical activity of chondroitin sulphates varied accordingly,[17] and that the chondroitin sulphate used in the commercial preparation Chondrosulf® 400 (CS400) differed from other chondroitin sulphates.

Considering the efficacy of this chondroitin sulphate in clinical trials, it seemed reasonable to expect, in real conditions, a decreased use of analgesics and antiinflammatory drugs in patients using chondroitin sulphate for at least 3 months. We therefore decided to look at co-prescriptions with CS400 in real-life conditions, in a pharmacy-based observational study of recent *versus* long-term users of Chondrosulf® 400 on the usage patterns of NSAIDs and analgesics, two years after its marketing.

We confirmed that long-term use of CS400 was indeed associated with less long-term use of NSAIDs.

2. Methods

This was a cross-sectional observational study of patients recruited in community pharmacies in France after purchase of CS400, over 20 weeks.

A random sample of 199 pharmacies was selected from the 1463 pharmacies in Aquitaine, South-West France. Each of the selected pharmacists was asked to include all consecutive patients with a prescription of CS400. A small financial incentive was offered to the pharmacists.

Every person who presented with a CS400 prescription to the pharmacy during the study period was eligible, if the prescription was for that person. Data were collected from the participant by the pharmacist, using a 10 item structured adhoc questionnaire that took 5 to 10 minutes to finish, after patient consent had been obtained.

The data collected were the demographic characteristics of the patient, previous medical history of gastric or duodenal ulcer. Medical history included the description of current and past use of CS400, of other Symptomatic Slow-Acting Drugs for Osteo-Arthritis (SSDO) such as glucosamine or diacerhein, and of analgesics or non-steroidal anti-inflammatory drugs identified from a closed list of drugs. The question asked was: "For disability caused by your osteoarthritis, have you ever used medication from this list?" A positive response to the above prompted further questions as to the name of the medication used, its dosage and duration of intake and dosage modification if any.

Information about potential contraindications of NSAIDs such as the concomitant use of oral anticoagulants, methotrexate and oral antidiabetics was also collected.