A herbal remedy, Hyben Vital (stand. powder of a subspecies of Rosa canina fruits), reduces pain and improves general wellbeing in patients with osteoarthritis—a double-blind, placebo-controlled, randomised trial.

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Abstract - The treatment of osteoarthritis, a disease that eventually affects the majority of the older population, involves the alleviation of symptoms such as pain and stiffness, and the reduction of inflammation. The double-blind, placebo controlled, crossover study reported here examined the effect of Hyben Vital, a herbal remedy made from a subtype of Rosa canina and recently reported to have anti-inflammatory properties, on the symptoms of osteoarthritis. One hundred and twelve patients with osteoarthritis were randomly allocated to treatment with either Hyben Vital 5 g daily or an identical placebo for 3 months, followed immediately by the alternative treatment. The patients assessed changes in joint pain and stiffness after each treatment period on a 5-point categorical scale. General wellbeing, including mood, sleep quality and energy were also assessed and recorded in a personal diary.

The results in the two arms of the crossover differed markedly. Group A (placebo first) showed significantly more improvement from Hyben Vital than from placebo, po0:0078 for pain ando0:0025 for stiffness. But Group B (Hyben Vital first) revealed a positive effect of the same order as for Hyben Vital in group A, not only from the active drug, but also from placebo (difference not significant). An identical pattern was observed when we evaluated general wellbeing from the diary records. When patients, on the basis of reduction in joint pain, were divided into responders and non-responders, the first 3 months of active treatment (group A) showed a response rate of 31/47 (66%) compared to that of placebo (group B) 18/50 (36%), po0:0185: No major side effects occurred in either group. The data indicate that Hyben Vital reduces the symptoms of osteoarthritis. We interpret the marked differences in the responses of the two groups as indicating a strong ''carryover'' effect of Hyben Vital. © 2004 Elsevier GmbH. All rights reserved.

Introduction - Inflammatory cells such as polymorphonuclear leukocytes are known to be causally involved in inflammation, in pain and tissue damage. The damage is caused by release of proteolytic and hydrophilic enzymes as well as toxic, reactive oxygen radicals derived from cells activated in the tissues and joints (Harris, 1988). The non-surgical therapy of osteoarthritis, a disease that attacks many of the middle-aged and the majority of the older population, involves alleviation of the symptoms associated with the disease, such as pain and stiffness, and the reduction of inflammation. Acetylsalicylic acid and a range of non-steroidal anti-inflammatory drugs including ibuprophen, indomethacin and naproxen, as well as glucocorticoids, have been used for the treatment of arthritis (Hochberg et al., 1995; Vane and Botting, 1998). These drugs have a variety of toxic and unwanted effects, including interference with haemostasis, gastric erosion and adverse effects on the liver and kidneys (Hochberg et al., 1995; Vane and Botting, 1998). Selective inhibitors of the cyclooxygenase- 2 system have recently shown promising analgesic and anti-inflammatory properties, without the side effects mentioned. They are, however, still expensive and a negative effect on the circulatory system cannot be excluded (Mukherjee et al., 2001). Recently, acetaminophen was shown to worsen the risk of upper gastrointestinal complications (Rodrigues and Hernandes- Diaz, 2001). There is, therefore, still a need for a safe, low-cost remedy for the long-

term treatment of symptoms in osteoarthritis. We have earlier shown that a standardised dry powder, Hyben Vital, made from the hips of a particular subtype of Rosa canina, reduced both chemotaxis and the generation of oxygen radicals in polymorphonuclear cells (Winther et al., 1999; Kharazmi and Winther, 1999). The plants used for the current preparation of Hyben Vital powder are grown in standardised fields according to good agricultural practice.

Harvesting takes place when the fruits are mature and all fruits are brought to freezing facilities without delay. Later, the selection of optimal fruits for production of the powder is made by a laser technique and the temperature of the subsequent controlled drying process never exceeds 40 C. The powder contains seeds as well as husks (Rosae pseudofructus cum fructibus) from a certain subtype of R. canina, by name LiTo, and is finally standardised to contain at least 500 mg Vitamin C per 100 g Hyben Vital powder. Further constituents are: pectins (total) 58.0 mg/g, b-carotene 57.9 mg/kg, b-sitosterol 0.5 mg/g, folic acid 1.6 mg/kg, Vitamin E 4.6 mg/100 g, Mg 170 mg/100 g, Zn 1.0 mg/100 g, copper 10.9 mg/100 g and non-quantified but reported flavonoids. The anti-inflammatory effect of the powder is not related to the well-known high vitamin C content of Rose hip extracts (Kharazmi and Winther, 1999). But we have earlier shown that, Hyben Vital modifies inflammation by reducing both chemotaxis and the generation of oxygen radicals in polymorphonuclear white cells (Winther et al., 1999; Kharazmi and Winther, 1999). Moreover, many volunteers have claimed that pain from osteoarthritis was diminished after a few weeks of treatment with the powder (Winther et al., 1999; Kharazmi and Winther, 1999). All these findings encouraged us to investigate whether Hyben Vital, in a larger controlled trial as now reported, would affect pain, stiffness and general wellbeing and the consumption of pain-reducing medicines, in particular paracetamol and the synthetic opioid Tramadol, in patients with osteoarthritis.

Methods

Patients - After we had obtained approval for the trial from the local Ethical Committee, 125 Caucasian out patients were enrolled through advertisements in local newspapers. The study was performed according to good clinical practice and designed to accord, as far as possible, with the guidelines on conduct of clinical trials on osteoarthritis devised by the Osteoarthritis Research Society International. The only notable exception was that the study included patients with arthritis of various joints instead of confining it to a single joint (Altman et al., 1996). The volunteers all gave their oral and written informed consent. They had all been earlier diagnosed by their own general practitioner or local rheumatologist as suffering from osteoarthritis, and were reported to have an X-ray verified diagnosis and symptoms of primary osteoarthritis in the hip, knee, hand, shoulder or neck, or some combination of these, for at least the last 12 months. All reported pain of the affected joints of at least mild to moderate severity. We excluded patients with liver or kidney disease and those known to suffer from allergy or a history of drug or alcohol abuse. We also excluded patients with cancer, rheumatoid arthritis, fibromyalgia, gout, serious cardiovascular disease, asthma requiring treatment with steroids, and any other disease which would substantially influence the patients' quality of life. Likewise, we excluded those who had received intraarticular hyaluronate, glucosamine sulphate, immunosuppressive drugs such as gold or penicillamine or injections of glucocorticoids within the 6 weeks prior to the study, and patients who were found to be unable to co-operate after the first evaluation.

Trial design - The trial was of a double-blind, placebo-controlled, crossover design, and randomisation of treatment allocation was performed in blocks of four with the block size unknown to the investigators. The design had three immediately successive periods: a 14 days run-in period followed by randomised allocation of the two treatment periods of 3 months each. The two primary efficacy parameters were: change in joint pain and the alteration of consumption of concomitant ''rescue'' medication for alleviating pain, evaluated after each of the two, blinded, 3-months
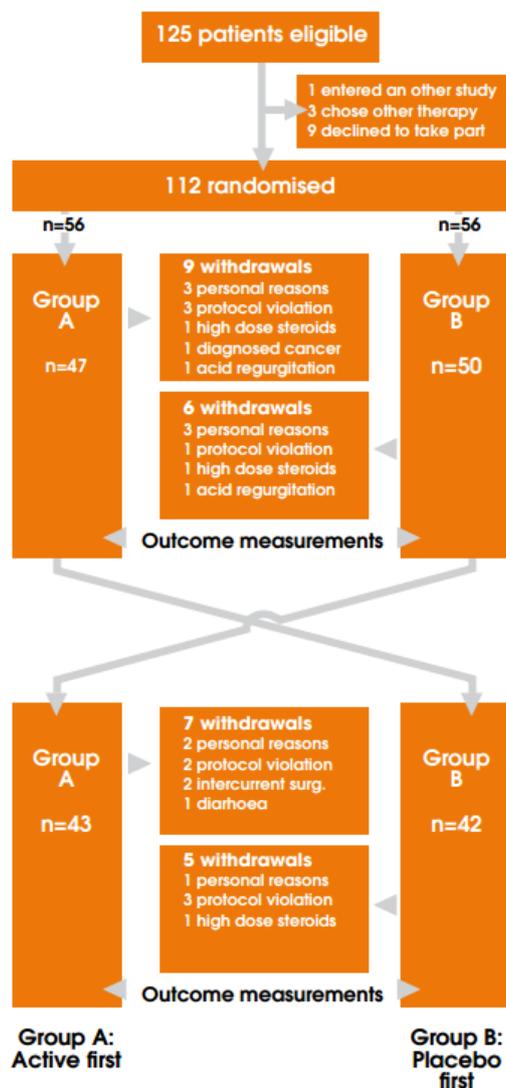
treatment periods. The three secondary efficacy parameters were: joint stiffness, general wellbeing including mood, energy and sleep quality, and a subjective overall evaluation of preference for one or other of the study medications. The run-in period was intended primarily for patients to become accustomed to the ideas of the trial, and to be instructed in and practise the daily subjective assessment/ record-keeping required, rather than as a formal ''baseline''. However, we took the opportunity during this period to measure blood pressure and removed a routine blood sample for measurement of haemoglobin, creatinine, sodium and potassium, blood glucose and cholesterol. The patients were then randomly allocated, in blocks of four, by a computer-generated allocation schedule, to receive capsules containing either a biologically standardised rose hip powder (Hyben Vital) or an identical placebo. The capsules were kept in numbered containers. The daily dosage was five 0.5 g capsules a.m. and p.m. One or other of the responsible investigators enrolled all patients. The patients as well as the research team were kept blind throughout the study. After 3 months, the groups switched immediately to the alternative treatment for a further 3 months. Immediately after each of the two treatment periods, a further routine blood sample was taken and blood pressure was measured. When the trial had been completed, all data were entered onto the spreadsheet, after which the treatment code was broken and patients were separated into two groups according to the treatment sequence they had received. It transpired that Group A started out with 56 randomised patients who took placebo first, followed by Hyben Vital, while Group B comprised the same number of randomised patients who took Hyben Vital first, followed by placebo (Fig. 1). The data for the two groups separately were also entered on the spreadsheet, which was then mailed to the statistician, who was also kept blind as to the treatment code.

Methods of assessing clinical effect
Primary efficacy parameters - The cardinal item of information obtained was the end-of-treatment subjective assessments of any changes in pain that had occurred during each of the treatments. These were estimated by the patients on a 5-step categorical scale ranging from 0 (no change) to 4 (almost total relief of pain). Here, the higher the score the greater the clinical benefit, a rise of 1 category representing 25% improvement. This technique also allowed us to calculate the number of responders and non-responders in each group. Each type of ''rescue'' analgesic consumed was noted daily by the volunteers in a diary. All patients taking NSAIDs regularly on prescription from their general practitioners were advised to continue such treatment, without any change in dosage, throughout the study. Three weeks into each of the two treatment periods we recommended the patients to reduce their consumption of concomitant pain-relieving medicine, if at all possible. Consumption of such medication was recorded daily in a diary, and at the end of each 3-monthstreatment period we calculated the consumption of each type of non-trial pain relieving medicine. As patients normally use a wide range of rescue medications, we simplified accounting of them by transformation into paracetamol equivalents, as devised by the Danish Health Authorities (Lægemiddelkataloget, 2002). Thus 25 mg of Tramadol and 25mg of codeine would be considered as equivalent to 1000 mg paracetamol and aspirin would be considered equal to paracetamol.

Secondary efficacy measures - The patients made a subjective assessment of joint stiffness at the end of each treatment period, on a 5-step categorical scale ranging from 0 (no change) to 4 (almost total relief of the symptom), as devised for pain. In addition, the patients made a daily subjective assessment of the severity of joint pain (in the morning and later in the day), stiffness (in the morning and later in the day) and the state of wellbeing, sleep, energy, and mood was recorded by the patient in a diary. Each aspect was assessed and recorded on a separate 10-point categorical scale, where an increasing score denoted increasing disability. An average of each kind of measurement was taken for statistical comparison of treatments.

Fig. 1. Flow-chart showing the dropout rate of the different time points of the study.

Patients' overall evaluation of the study medication - On the final day of the trial, before the treatment code had been broken, the supervising physician asked this question of the patient: Taking all aspects into consideration, did you develop a definite preference for one of the treatments, or not?

Statistical techniques - We based the sample size on results from an earlier clinical trial using the same dry powder. Data from all the randomised patients were entered on the spreadsheet. Statistical evaluation was based on the intention to treat (ITT), with the last value carried forward. We applied Wilcoxon's test for matched pairs when evaluating the study as a simple crossover trial and when we compared effects occurring within the same group of patients. The Mann–Whitney test was applied to comparison of groups A and B after 3-months treatment. The only exceptions were simple yes/no questions, to which Fisher's test was applied. Data given are mean ±SD. Any p value equal to or <0.05 was regarded as statistically significant.

Results

Description of patients - Of the 125 eligible patients who responded to our advertisement, we eventually enrolled 112, including 71 women, mean age 68 years (range 33–93) and 41 men, mean age 64 years (range 35–89) (see flow diagram of Fig. 1).

Matching of groups - Details are given in Table 1. The two groups were virtually identical in their demographic data, in the severity and distribution of osteoarthritis and in their consumption of rescue medication; indeed, there was no significant between-group difference in any of the 16 items of Table 2. The mean body mass index for the included patients was 26.9, range 18–42 kg/m2 . Although only 85 patients completed the trial, the two final groups of per-protocol patients were still not significantly different. We consider the groups therefore to have been very well matched (Table 1). Fifteen patients dropped out before the first 3 months period was finished, leaving 97 patients for the second part of the study and 85 completed both treatment periods (Fig. 1). Before the code was broken, a further 5 were excluded because of protocol violation detected on evaluation of the patient's record form before the data were entered on the spreadsheet. This left 80 patients, 46 women and 34 men, for a per-protocol analysis. Of the randomised patients, 59 had arthritis of the knee, 46 of the hip, 40 had involvement of the hands, 18 of the neck and 14 of the shoulder or a combination of these different joints. The dropouts were correspondingly represented by all the different joints mentioned and there were no major disagreements between the ITT and the per-protocol analysis—hence we refer only to the ITT analysis if not otherwise stated. Of the included patients, 40 were taking NSAIDs regularly, 40 paracetamol, 12 Tramadol, 3 codeine, 2 Aspirin, 2 morphine, and 1 dextropropoxyphen. Thirty of the patients took no rescue medication whatever. When a subanalysis of the initial values of the placebo first group (n ¼ 56) versus the active treatment first group (n ¼ 56) were made, there were no significant differences in body mass index, age, sex, joints involved, consumption of NSAID and rescue medication (Table 1).

Table 1. Baseline demographic and osteoarthritic characteristics of the study population

	Intention-to-treat population		Per-protocol-population	
	Placebo treatment (n = 56)	Active treatment (n = 56)	Placebo treatment (n = 39)	Active treatment (n = 56)
Age (years)	66.8 ± 11.8	67.1 ± 11.6	67.5 ± 10.6	67.0 ± 10.8
Sex				
Women	34	37	21	26
Men	21	20	18	15
BMI (kg/m2)	26.8 ± 5.0	27.7 ± 4.9	27.7 ± 4.9	27.5 ± 5.5
No. of patients with OA of the hip	20	26	15	21
No. of patients with OA of the knee	30	29	24	24
No. of patients with OA of the neck	11	7	10	6
No. of patients with OA of the shoulder	7	7	6	6
No. of patients with OA of the hand	17	23	15	19
No. of patients on NSAIDs	20	20	17	19
No of patients on paracetamol	21	19	18	16
No. of patients on tramadol	7	5	6	4
No of patients on codein	1	2	0	0
No of patients on aspirin	1	1	1	1
No of patients on morphine	1	1	1	1
No of patients on dext. ppox. phen.	1	0	0	0
No. of patients with no medication	26	24	19	18

Compliance - Compliance, as calculated from the proportion of study medication (number of capsules) returned by the patients, was 92.8 ± 11% for Hyben Vital and 90.6 ± 11% for placebo (nonsignificant difference). Compliance in the placebo-first group was 92.3 ± 10.0% and for active treatment first 90.5 ± 8.0% (nonsignificant difference).

Primary efficacy measures: pain - Details are given in Table 2. The most important item of clinical information—the patients' final evaluations of change in pain—showed a remarkable difference between the groups. In group A (placebo first), there was a highly significant difference in favour of Hyben Vital—a mean rise from 1.02 ± 1.45 after placebo (an improvement of 25%), to 1.91 ± 1.43 (an improvement close to 50% of the improvement scale) observed after 3 months of Hyben Vital treatment, P<0.0078. But group B (starting with active treatment) showed no significant difference between the two treatments: 1.45 ± 1.28 units for active treatment, as compared with 1.72 ± 1.37 for placebo, p = 0.6084. Table 2, upper panel, and the histograms of Figs. 2A and B illustrate the large between-treatment differences, when groups A and B are compared. Group A patients showed a marked difference between the two treatments at every degree of response, while B showed no consistent pattern of difference between treatments. The carryover effect that we postulate as responsible for this between-groups discrepancy (see also Discussion) likewise blunted the level of significance when the two treatment groups were lumped together: there was again no significant difference between the effects of the two treatments (p<0.0991), data not shown. An evaluation of between- group differences after only 3-months treatment did not attain statistical significance, although an improvement of 50% was observed in favour of active treatment (p<0.101) data not shown.

We also made an alternative analysis of the data by identifying two categories of subject ''responders'' who by definition showed at least one category of improvement and ''nonresponders'', who showed less improvement than this. If we compare the A and B groups after the first 3 months of treatment, the overall outcome of the analysis is that 31/47 (66%) of subjects responded to Hyben Vital, while 18/50 (36%) responded to placebo and this was significant at (p<0.0128). The corresponding per-protocol evaluation yielded a p value of 0.0428.

Table 2. Pain given on a scale from 0 (no reduction) to 4 (almost total relief of pain), consumption of rescue medication given as paracetamol equivalents (g)
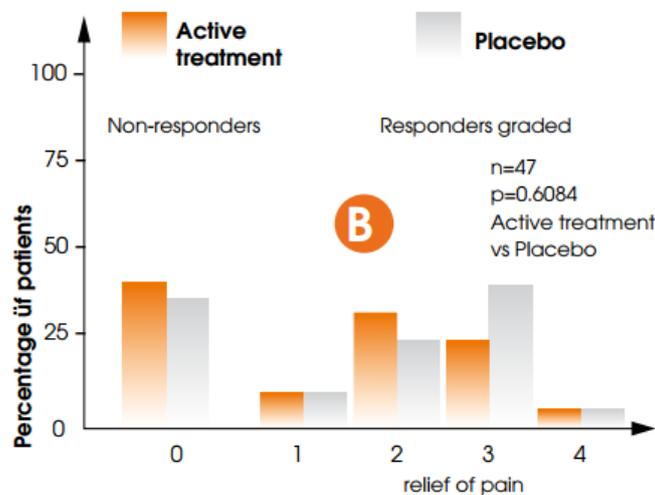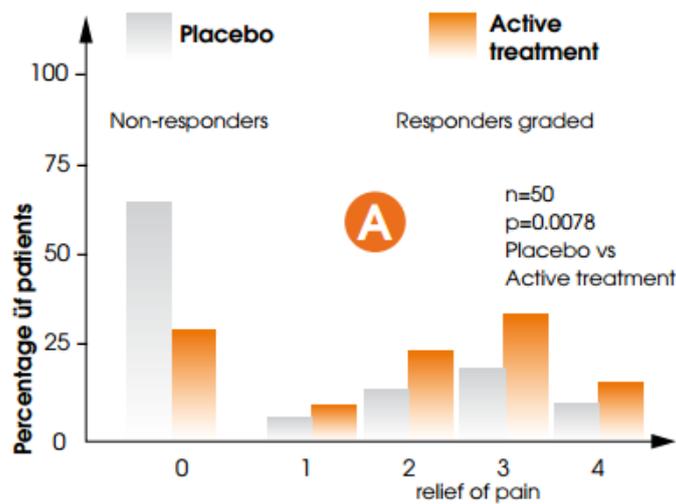
	Placebo	Active treatment	p-value
Group A: Placebo first, then active treatment			
Pain	1.02 ± 1.45	1.91 ± 1.43	0.0078
Rescue medication	227.40 ± 249.50	127.90 ± 143.30	0.0024
Stiffness	0.91 ± 1.38	1.91 ± 1.25	0.0025
Group B: Active treatment, then placebo			
	Placebo	Active treatment	p-value
Pain	1.45 ± 1.28	1.72 ± 1.37	0.6084
Rescue medication	127.50 ± 94.00	77.70 ± 51.1	0.1452
Stiffness	1.28 ± 1.35	1.71 ± 1.47	0.3850

Stiffness estimated on a scale from 0 (no reduction) to 4 (almost total relief of stiffness) is given for groups A and B. Data given are mean ±SD.

Primary efficacy measures: pain - Twenty-three patients handed in medical diaries adequate for ITT analysis of their use of NSAIDs in accordance with the protocol. Consumption during the two treatment periods was found to be identical (data not shown). Paracetamol and acetylsalicylic acid were administered as 500 mg tablets and Tramadol and codeine as 50 and 25 mg tablets, respectively. Twenty five patients handed in medical diaries adequate for ITT analysis of their daily use of paracetamol and seven and four and two patients, respectively, handed in diaries adequate

for ITT analyses of their daily use of Tramadol, codeine and Aspirin. A pattern very much like that previously described for pain, occurred. Group A, placebo first, data available from 12 patients, showed after 3 months a mean consumption of 227.4 ± 249.5 g. However, this consumption was reduced to 127.9 ± 143.3 g after 3 months of active drug treatment. This decline of 99.4 ± 163.9 g (p<0.0024) comprised a 44% reduction. The B group, active treatment first, with data available from 15 volunteers, showed after the first 3 months of active treatment a mean value of 129.50 ± 91.00 g, a value close to what was observed in the second active treatment phase of the group A patients (see Table 2). A further 3 months placebo treatment, in the B group, resulted in a non-significant decline to 77.70 ± 51.1 g (Table 2). No significant change was present when the two groups were lumped together (p<0.1420), data not shown.

An evaluation of the two groups after 3-months treatment showed placebo values of 227.4 ± 249.5 g and active values of 128.4 ± 94.3 g. The reduction, in favour of active treatment, was 44%, but was not statistically significant. When, however, a subanalysis was made on the delta change in consumption of rescue medication from the beginning of each of the two 3-months treatment periods (the two initial weeks of treatment) to the end of each of the respective periods (the final two weeks of the 3-month treatment period), there was a significant reduction in consumption of rescue medication from active treatment, when comparing placebo and active treatment (p<0.006), data not shown.

Fig. 2. (A) Histograms comparing, in group A subjects (placebo first then Hyben Vital), the degree of improvement in pain relief from placebo (white columns) as compared with Hyben Vital (shaded columns). The height of each column indicates the percentage of patients who experienced pain relief of category 0, 1, 2, 3 or 4, corresponding to 0%, 25%, 50%, 75% or 100% relief of pain (p value refers to the added scores comparing the two different treatments). **(B)** Histograms comparing in group B subjects (Hyben Vital first then placebo), the degree of improvement in pain relief from Hyben Vital (shaded columns) as compared with placebo (white columns). The height of each column indicates the percentage of patients who experienced a given pain relief of category 0, 1, 2, 3 or 4, corresponding to 0%, 25%, 50%, 75% or 100% relief of pain (p value refers to the added scores comparing the two different treatments).

Secondary efficacy measures - Joint stiffness, tested on a scale from 0 (no improvement at all) to 4 (almost total relief of stiffness) revealed an almost identical pattern to that found for pain. In group A, the initial placebo value was 0.91 ± 1.38 (an improvement of 23% on the scale) as compared to 1.91 ± 1.25 (an improvement of 48%) while on Hyben Vital therapy), $p0.0025$. Group B, however, showed no significant difference between treatments: Hyben Vital 1.28 ± 1.35 versus placebo 1.71 ± 1.47, $p < 0.3850$ (Table 2). Nor was there any significant difference when the two groups were taken together ($p < 0.1612$) data not shown. A comparison of the two groups after 3 months of treatment, although in favour of active treatment, did not attain statistical significance ($p < 0.153$), data not shown. The diary records of joint pain and stiffness in the morning and later in the day, wellbeing, mood, energy and sleep, available in diaries from 47 patients, showed the same sharp distinction between groups as for the primary parameters. The placebo-first group A (n = 26) showed, in all measurements a distinct difference in favour of Hyben Vital. The change was highly significant, stiffness and pain in the morning giving p values of 0.0016 and 0.0127, respectively, and sleep quality, mood and general wellbeing, 0.0096, 0.0124 and 0.0164, respectively. But in the Hyben-first group B, the two sets of results appeared indistinguishable, and there was not a single instance of anything approaching a statistically significant difference between the two treatment groups, as shown by a mean p level of more than 0.50 (details not shown). The majority of the significant changes observed in favour of active treatment in the placebo-first group, were confirmed, when subanalysis comparing the A and B group after 3- months treatment was made: stiffness in the morning, $p < 0.054$; pain in the morning, $p < 0.036$; general wellbeing, $p < 0.012$; mood. $P < 0.017$; and sleep quality, $p < 0.005$.

Patients' preference for treatment - The separate groups again showed a large difference, similar in pattern to that described above. In group A, 24 patients reported that they felt most improvement from Hyben Vital, while 8 patients preferred placebo and 9 were not sure ($p < 0.0070$). In group B, 12 patients preferred the first treatment (Hyben Vital) whereas 20 voted for placebo treatment and 8 did not have any preference ($p < 0.2153$). Comparison of the A and B groups (Fisher's test) gave a p value of < 0.004 in favour of Hyben Vital.

Routine screening tests - Haemoglobin, blood glucose, creatinine and sodium and potassium levels were unaffected by either treatment. Nor were there any changes when those patients with blood glucose levels above 5.5 mmol/l were analysed separately. An unexpected finding was that Hyben Vital resulted in a small but significant 8.5% fall of total cholesterol.

Unwanted effects - Although 27 of the original 112 subjects recruited dropped out during the 6-months treatment period, only 3 of these defaulted because of adverse effects: acid regurgitation occurred in one patient during placebo therapy and in one during active treatment, and one other patient with diarrhoea dropped out while on placebo; for details see Fig. 1. In the remaining group there were 12 who reported milder unwanted effects. These were as follows: frequency of micturition 4 (three while on active treatment and one while on placebo); waterbrash 3 (present in

both treatments); diarrhoea 2 (present in both treatments); constipation 2 (1 during placebo and 1 during both treatments); urticaria 1 (while on placebo). There were no major side effects of any kind in the whole group.

Discussion

Interpretation of trial results - The chief advantage of a crossover trial, as used here, is that in comparing the effects of two successive treatments on the same ''arm'' of the trial, each patient acts as his/her perfect control, so concern about mismatching of the groups—an important source of error—can be forgotten. A wholly uncomplicated crossover trial with a positive result can be expected to yield three pieces of information: a withingroup significant comparison of the two test substances—one from each of the two arms of the trial (and more or less identical with each other), and a significant between-groups comparison at the crossover point, provided that the groups have been well matched, since in this case the patients do not act as their own controls.

Looking at the results of the trial described here, it is obvious that they are far from this idealised pattern. That arm of the trial given placebo first does show a significant, clear-cut difference between the effects of the two test substances. So far so good, but the other arm— active substance first, placebo second—shows no significant difference between the two. We believe that by far the most likely explanation of this discrepancy between the two arms of the trial is a strong ''carryover'' effect of Hyben Vital. This is a common, major complication of crossover trials and the reason for the inclusion of a ''washout'' period after crossover.

The usual tactical response is to write off all data after the crossover point and to supplement the single within group result obtained in the placebo-first arm, with a between-groups comparison at the crossover point. But this, using the primary efficacy data of Table 2, also gave a non-significant result. This raises the possibility that a carryover effect is not the whole explanation—a slow onset of the active drug effect could be another factor. The strength and significance of the difference between placebo and active drug seen in Group A is supported by several ancillary aspects. If the reduction in pain sensation was evaluated after 3-month treatment on a yes/no basis, there was a significant reduction of pain from active treatment when compared to placebo. In agreement with this finding, preference for treatment A or B was also in favour of active treatment and the diary recordings on pain, general wellbeing, mood and sleeping quality were all statistically significant in favour of active treatment. Taken together these findings seem to fully justify confirmation of the action of Hyben Vital by a large-scale, parallel, placebo-controlled, blind study, and this is our intention.

R. canina (the ''dog rose'', the common wildbriar rose of English hedgerows) is said to have been so named because the ancient Greeks believed its root to be effective against the bite of a mad dog (Brewer, 1981). In this context, Pliny the Elder used the plant's classical Greek name ''cynorrhodos'', combining the verbal roots of ''dog'' and ''red'' (Pliny, 1966). Although Hyben Vital has been marketed in Scandinavia for several years, modern European interest in the plant has been concentrated on preparations made from the hips rather than the root, mainly because of their high content of vitamin C, and herbal tea infusions of ''cynorrhodon'' are still used today.

It is widely known that rose hips contain significant amounts of vitamin C, but it seems highly unlikely that this accounts for much, or indeed any, of the activity of Hyben Vital in this trial. A large-scale study in 1996 on the Framingham population group showed that the middle and highest tertiles of daily dietary vitamin C intake did protect against the long-term progression of knee osteoarthritis (especially against loss of cartilage). But the lowest intake tertile—a daily mean of 81 mg for men and 94 for women— had no such protective effect (McAlindon et al., 1996). The vitamin C content of a Hyben Vital dosage of 5 g daily, as used in this trial, is only 26 mg, i.e. only one-third of

the Framingham lowest tertile and therefore very unlikely to contribute significantly to the action of Hyben Vital.

We have earlier shown that Hyben Vital significantly reduces the migration of neutrophils, when estimated after 1 month of treatment (Winther et al., 1999; Kharazmi and Winther, 1999). One explanation for the lessening of symptoms during Hyben Vital treatment could therefore be a reduction of the inflammation that is an integral part of the pathogenesis of osteoarthritis (Harris, 1988). This hypothesis has gained increasing interest, as an active ingredient that inhibits neutrophil chemotaxis, has now been isolated from the present subtype of Rose hip (Larsen et al., 2003). If the present suggestion is correct, it could also explain the pronounced carryover effect; once inflammation has subsided, it requires a certain interval of time before the process can be reactivated. As rose hips have been used in daily household use for centuries, it is surprising that their anti-inflammatory property has not been detected before now. A possible explanation is that different species of Rose hip vary in their anti-inflammatory properties (Brandt and (Akesson, 2002). In another study testing a possible interaction between Rose hip and warfarin, we could not show any effect on coagulation and platelet aggregability (Winther, 2000). This suggests that Rose hip, unlike NSAID, aspirin and ginger—another natural remedy also used for symptoms of osteoarthritis (Altman and Markussen, 2001)—does not affect the arachidonic acid and cyclo-oxygenase system. This could explain why the incidence of side effects is lower for Hyben Vital than for the therapies mentioned above.

Conclusion - We have found that the herbal remedy Hyben Vital has a moderate alleviating effect on joint pain and improves general wellbeing, sleep quality and mood in patients with osteoarthritis, without producing any side effects. We consider that the results warrant a largescale double-blind, long-term, placebo-controlled and parallel study of Hyben Vital.

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