REVIEW ARTICLE

Use of non-steroidal anti-inflammatory drugs in the preven tion of Alzheimer's disease in the high risk patient.

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Alzheimer's disease (AD) is a major neurological disorder causing dementia in th elderly. Because the causes of AD are not known, there is no real treatment for th disorder. However, a number of risk factors have been associated with AD. Amon these factors, a family history of AD is most significant. An inverse associatio between non-steroidal anti-inflammatory drugs (NSAIDs) use and AD has been previousl demonstrated in several epidemiological studies. Here the potential use of NSAIDs as a pr tective measure for individuals in high risk groups is suggested.

INTRODUCTION

Dementia is an age-related disorder. It has become a major health problem because of the worldwide increase in the elderly population, especially those 80 years of age or older. This increase in the elderly population presents a serious health problem for Canadians. According to the 1991 census 13.8% (3,157,500) of the Canadian population are aged 65 and over (1). Among this population, the prevalence of dementia was estimated to be 8.0% (252,600) (2). It was suggested that if the prevalence estimated remains constant, the number of Canadians with dementia will rise to 592,000 by the year 2021(2).

Failure to learn and loss of analytical ability are the neurological signs of dementia. Patients are alert and attentive to a given task but fail because of memory deficits. Due to these neurological dysfunctions, people with dementia lose the ability to work and to manage their daily lives.

Many different conditions have been associated with dementia. The most prevalent causes of dementia are Alzheimer's disease (AD) and vascular dementia (3). In the Rotterdam study (4), AD accounts for about three quarters of all cases of dementia. There is at prese no treatment for AD, although nerv growth factor and cholinergic analo have been used in attempt to reduce th cholinergic neuronal death and to resto cholinergic function. Present interve tions are mainly aimed at maintainin skills and reducing behavioural distu bance by using programmes includin cognitive training or environmental red sign as well as caregiver training (5).

Although the causes and th mechanisms of AD are still unknown, great amount of work has been devote to identifying major risk factors associate with AD. As discussed below, epidemi logical studies, as well as genetic studie have demonstrated that certain condition could predispose individuals to AD (6-9 Recent case-control and population base studies (10, 11) suggest the potential us of anti-inflammatory drugs in the preven tion of AD. Due to the lack of treatmen for AD, possible prevention or delayin development of AD will provide hope fo individuals in high risk groups.

In this paper, the risk factors asso ciated with AD will be presented. The potential of NSAIDs in preventing AD i high risk individuals will be discussed.

RISK FACTORS OF AD

Both genetic and epigenetic factor have been suggested to be risk factors as sociated with the development of AD.

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1. Genetic hypothesis

There is now strong evidence for the association of genetic factors with AD. The tendency of clustering of AD patients among close relatives has been reported in many studies (8, 9). Case-control studies have shown a significant association between the presence of dementia among first-degree relatives and AD (12). Not all AD patients, however, had such familial aggregation. Nevertheless, patients with an earlier age onset of AD are more likely to have relatives with AD than are patients with a later age onset of the disease (13). It has been suggested that an onset of age 70 be used to differentiate individuals whose relatives were at higher risk from those whose relatives were at lower risk (13).

Three genetic loci have now been identified that predispose to AD: AD1 on chromosome 21, AD2 on chromosome 19 and AD3 on chromosome 14 (14). A small percentage of individuals suffering from familial AD are known to possess mutations in the gene encoding a protein known as the amyloid protein precursor or APP. These mutations are autosomal dominant and are localized on chromosome 21 (15). It has long been recognized that another genetic abnormality, Down syndrome (trisomy 21), is closely associated with early and severe development of AD neuropathology (16). A larger percentage of patients with familial AD are found to have a specific locus on chromosome 14 (7). This gene has recently been identified and it encodes a protein with multiple putative transmembrane domains. However, the physiological function of this protein is not yet known.

The majority of AD is non-familial and is of late-onset or sporadic form. It is now recognized that possession of one or two copies of the E4 allele of the apolipoprotein E gene, which is located on chromosome 19, is a risk factor for this form of AD (17, 18). However, it should be noted, however, that the apolipoprotein E gene is not a disease locus (i.e. specific mutationsin this gene do not cause AD).

The association of apolipoprotein E gene with AD has been challenged by one study (19). In this study, the prevalence of apolipoprotein E gene was examined in both AD and non-AD dementia patients. The results suggested that the E4 allele of the apolipoprotein E gene is not unique to AD and that the importance of this gene as a risk factor for AD should therefore be reconsidered.

2. Environmental risk factors

Genetic factors alone cannot account for all cases of AD. Environmental risk factors may also play a major role. There is evidence that head trauma could be a contributory factor. An history of head injury was found in 20% of the familial AD and 43.5% of sporadic AD cases compared to only 2.9% in control group (20). Based on these results, the authors hypothesized that head injury was more common among AD patients without a genetic risk for the disease (20). On the other hand, severe headache and smoking have an inverse relationship with AD (21, 22).

Although aluminum toxicity has not been ruled out as a contributory factor, there is little evidence for a causal link. Experimental studies have demonstrated an aluminum-induced chronic myelopathy in rabbits and the development of neurofilamentous lesions after low-dose aluminum administration in cell culture (23). Other evidence in support of aluminum as a risk factor for AD has been inconsistent (24-27).

Recently, studies have shown an inverse relationship between levels of education and the prevalence of dementia and AD. In a survey in China, the prevalence of both dementia and AD decreased from 6.9% in illiterate persons to 1.2% in those with over 6 years of education (28). Similar results have been reported in other studies (4, 29, 30, 33). Katzman hypothesized that education can result in decreased risk of AD (31). However, this hypothesis has not received full support. Cobb *et al.* (32) suggested that while incidence rates were significantly elevated for AD and non-AD dementia among the least educated, low educational attainment, after age adjustment, was not a significant risk factor for the incidence of general dementia or of AD.

Some retrospective studies have reported an association of Parkinson's Disease (PD) with AD (34). A recent prospective cohort study concluded that patients with PD, especially those with severe extrapyramidal signs, have twice the risk for the development of dementia than control subjects (35).

3. Other risk factors

A history of depression and other psychiatric disorders has been suggested as a risk factor for dementia, especially for AD (54). It is generally accepted that the age-specific incidence of AD is higher in females than in males. Hypothyroidism has also been suggested as a strong risk factor for AD (55).

On the other hand, rheumatoid arthritis (9) and smoking (22) seem to reduce the risk of developing AD. It is possible that the decreased risk of AD among smokers might be due to the potential action of cigarette nicotine on nicotinic receptors in the central nervous system (36, 37). The inverse relationship of arthritis and AD, which will be mentioned later, may imply a protective role of non-steroidal anti-inflammatory drugs (NSAIDs), since NSAIDs are widely used in arthritis patients.

In summary, among the many factors associated with AD, a strong family history of dementia is a risk factor for AD, even though the majority of AD is of non-familial form. Education, arthritis and smoking have been found to reduce the risk of AD.

SHOULD NSAIDS BE USED TO PREVENT AD IN HIGH RISK SUBJECTS?

A significant inverse association of anti-inflammatory drugs (NSAIDs and corticosteroids) and AD was recently reported in a preliminary co-twin control study (10). Following this report, at least two articles have been published in support of the possible protective roles of NSAIDs in AD (11, 38). Earlier evidence in support of an inverse relationship between anti-inflammatory drugs and AD included the low prevalence of AD among patients with arthritis (9, 39), as mentioned earlier. Jenkinson *et al.* (39) reported that only two cases of rheumatoid arthritis cases were found in 96 patients with AD senile dementia, while 12 rheumatoid arthritis cases were found in the same number of controls. The subjects in this study were all aged over 65 years. The relative risk for AD in NSAID users was estimated to be 0.38 compared with all non-users (11). The protective effects of NSAIDs for AD as well as on the cognitive impairment of patients clinically diagnosed with AD (38) suggest that these medications may serve as important interventions to prevent or delay the onset of AD in people who are in high risk groups.

1. Rationale for using anti-inflammatory drugs

Recent evidence has indicated that activation of inflammatory and immune mechanisms accompanies the degenerative process of AD. A characteristic histological hallmark of AD is the presence of senile plaques, consisting of degenerating neurites and amyloid plaques in the brain. A complement-mediated inflammatory response has been reported at both diffuse amyloid plaques and degenerating neurites in AD brains (40-42). This was suggested to represent an early stage in plaque development (41). These acute inflammatory changes are proposed to result in the development of AD pathology or they may be the result of the degenerative process (43). One major component of senile plaque is amyloid b protein, a proteolytic fragment of amyloid precursor protein (APP) (41, 44). It was suggested that APP itself may be an acute phase protein, a normal serum protein whose expression is dramatically influenced by interleukin-1 (IL-1) and interleukin-6 (IL-6) during acute phase response to inflammatory activity (45). As primary mediators of the acute phase response, cytokines, such as IL-1, IL-6 and tumor necrosis factor, have been implicated as being involved in the pathophysiology of AD (46, 47).

Chronic inflammatory reactions, such as the accumulation of reactive microglia, which are the predominant inflammatory cell population in the central nervous system, have been observed in senile plaques (41, 48). These microglia are antigen-presenting cells which express class II major histocompatibility antigen HLA-DR (49, 50). Microglia have demonstrated immunoreactivity to IL-1 and tumor necrosis factor (50).

The presence of acute phase proteins, cytokines, complement and microglia in amyloid plaque, which are usually seen during the immune response, suggests that inflammatory processes might be responsible for the pathophysiology of AD. Based on this theory, therapeutic intervention with anti-inflammatory drugs should alter or slow down the neurodegenerative process in AD.

2. Potential impact of NSAIDs on AD

Because no curative treatment for AD is available at the present, the potential use of NSAIDs in preventing or delaying the development of AD could become a useful intervention for populations at high risk, such as individuals with a strong family history of AD. Preventive use of NSAIDs in these high risk individuals might reduce the prevalence of AD when these individuals enter elderly age (80 years or over). Let us assume that Andersen's (11) relative risk of 0.38 for AD in NSAIDs users compared with non-users could be applied to the Canadian population. By using NSAIDs as a preventive intervention, the prevalence of AD could be reduced to 1.5% in those aged 65 and over, compared with the prevalence of 5.1% of AD in the same population group without the intervention (2). Indeed, sustained use of NSAIDs was reported recently to be associated with delayed onset and reduced risk of AD among siblings at high risk of AD (51).

3. Future studies

Early studies attempting to establish the preventive role of NSAIDs in AD were mainly using retrospective methods (11). Even in cohort studies, population samples consisted of patients who were clinically diagnosed as having probable AD (38). To evaluate the protective effects of NSAIDs in high risk groups, prospective cohort studies will provide stronger evidence from which to draw a conclusion. The first step in the evaluation process is to identify subjects with a strong family history of AD. Because familial AD has the tendency of early onset, these individuals have a high risk to develop AD by age 50. Therefore, it is ideal to follow these individuals before they reach age 50. The second step is to randomly divide the subjects into two groups, the treatment group who will be given NSAIDs as a preventive measure and the non-treatment group who will receive placebo treatment. Alternatively, the treatment group could be the subjects who are willing to take NSAIDs and the non-treatment group are those who are not willing to take NSAIDs. The cognitive functions of the two groups could be assessed blindly over the years by a specialist. A significantly lower incidence rate of AD in the NSAIDs treatment group compared to the non-treatment group would support a preventive role for NSAIDs in the development of AD. Although it would take some time before the preventive role of

NSAIDs could be confirmed by such cohort study, the potential protective role of NSAIDs could at least provide individuals at high risk some hope or a choice in controlling the quality of their future life.

4. Cautions with NSAIDs

As a prophylactic measure to prevent AD or delay the progress of AD, chronic administration of medication would be required. Although NSAIDs have fewer systemic toxic effects than corticosteroids, the known adverse effects of NSAIDs are still serious drawbacks for routine use of these drugs as a prophylactic measure.

Gastrointestinal side effects, such as gastric upset, abdominal pain, gastrointestinal hemorrhage and pancreatitis have been well documented for NSAIDs use. NSAIDs can also cause serious renal dysfunction. Acute renal failure in children (52) and acute interstitial nephritis (53), as well chronic renal insufficiency(53) have been reported with NSAID use.

It is important to consider the pros and cons of NSAID use to prevent AD in potential AD patients. It is therefore necessary to examine the risk factors related to each individual. As suggested in this paper, only populations at high risk should be considered as candidates in using these drugs as preventive means. The severe adverse effects of NSAIDs on gastrointestinal and renal function dictate that periodic follow up for chronic NSAID users.

CONCLUSION

AD is a progressive neurodegenerative disease. The main interventions at the present are palliative management. Only recently has the inflammatory pathophysiology of AD been revealed by cellular and molecular studies. From the emerging studies of the past five years regarding NSAIDs and AD, we may soon understand the mechanisms by which NSAIDs prevent AD progression.

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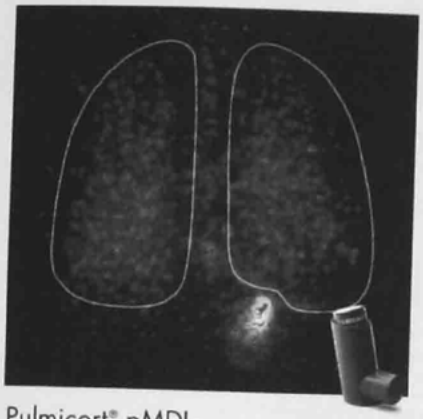

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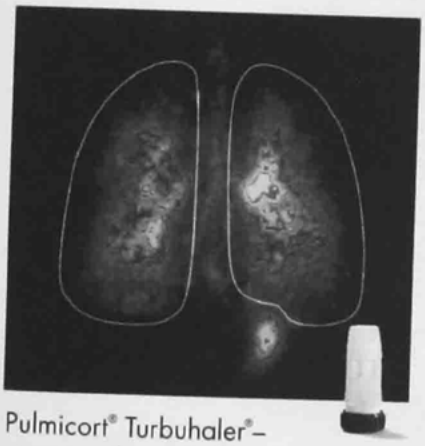

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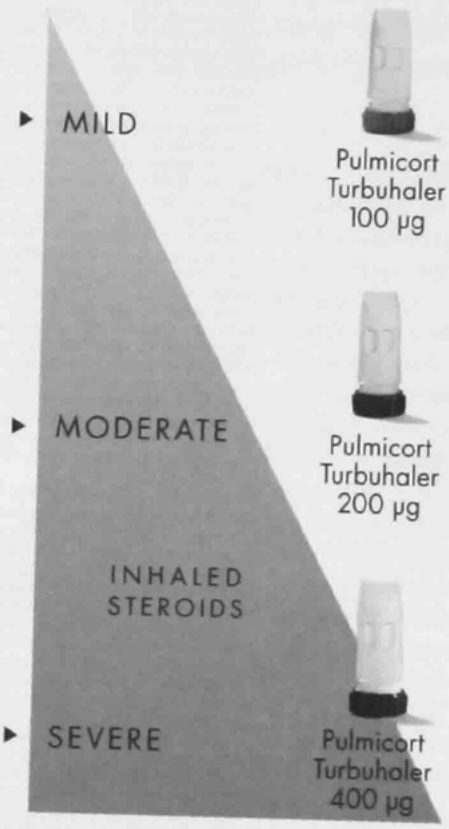

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CONTRAINDICATIONS: 1. Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis, 2. Hypersensitivity to budesonide, 3. Active or quiescent pulmonary tuberculosis, 4. Untreated fungal, bacterial or viral infections of the respiratory system.

WARNINGS: 1. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids; therefore particular care is needed in patients who are transferred from systemically active corticosteroids to PULMICORT (budesonide). After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although PULMICORT may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level. Patients previously on high doses of systemic steroids may regain earlier symptoms not related to asthma such as rhinitis and eczema when transferred from oral therapy to PULMICORT. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. Temporary resumption of systemic steroids may be necessary to treat these conditions. 2. The development of pharyngeal and laryngeal candidiasis is cause for concern because the extent of its penetration of the respiratory tract is unknown. If oral pharyngeal candidiasis develops, appropriate anti-fungal therapy should be implemented to eradicate the infection. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each inhalation. (See DOSAGE AND ADMINISTRATION). 3. Glucocorticosteroids may mask some signs of infection and new infections may appear during their use. 4. PULMICORT is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm. Patients should be instructed to contact their physicians immediately if episodes of asthma not responsive to bronchodilators occur. 5. There is no evidence that control of asthma can be achieved by administration of PULMICORT in doses higher than those recommended. During such episodes, patients may require therapy with systemic corticosteroids.

PRECAUTIONS: 1. In transferring patients from a systemic steroid to PULMICORT (budesonide), the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression), may occur in spite of maintenance or improvement of respiratory functions. (See DOSAGE AND ADMINISTRATION). 2. It is essential that the patient be instructed that PULMICORT is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack. 3. The long-term effects of budesonide on developmental or immunologic processes in the mouth, pharynx, trachea, eyes, and lung are unknown. With the recommended therapeutic doses of PULMICORT, there is little risk of adverse systemic effects. 4. Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually. 5. Pulmonary infiltrates with eosinophilia may occur in patients on PULMICORT therapy. Although this is possible in some patients who are administered inhalational steroids, their causative role cannot be ruled out. 6. **Usage During Pregnancy.** Administration of PULMICORT during pregnancy should be avoided unless there are compelling reasons. In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and in mice. The relevance of these findings to humans has not yet been established. In the absence of further studies in humans, budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypo-adrenalism. 7. **Lactation.** Glucocorticoids are secreted in human milk. It is not known whether budesonide would be secreted in human milk, but it is suspected to be likely. The use of PULMICORT in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the mother, or infant. 8. **Children Under 6 Years of Age.** PULMICORT is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group. 9. Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and height (in children) should be periodically assessed. 10. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids. 11. There may be enhanced systemic effects of budesonide in patients with an advanced liver cirrhosis, and in those with hypothyroidism. 12. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. 13. Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops treatment with antiviral agents may be considered. If, however, a viral upper respiratory infection is present, the patient should adhere to the regular asthma medication. In patients who are known to deteriorate rapidly when they have a viral respiratory infection, a short course of oral corticosteroid therapy should be considered. Clinical studies have shown that viral infections cause significantly fewer problems in patients who are on regular treatment with topical glucocorticosteroids. 14. To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of PULMICORT TURBUHALER.® 15. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as Candida albicans. (See DOSAGE AND ADMINISTRATION).

Drug Interactions: The kinetics of budesonide were investigated in a study of healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance.

ADVERSE REACTIONS: No major side effects attributable to the use of PULMICORT (budesonide), in all dosage forms, have been reported. During clinical trials, the frequency of subjectively reported side effects was low. The most common side effects were cough, throat irritation, and hoarseness (2-4%). Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. Skin reactions (urticaria, rash, dermatitis, etc.) may, in rare cases, occur in association with local corticosteroid therapy. Psychiatric symptoms such as nervousness, restlessness and depression, as well as behavioural disturbances in children, have been observed. As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted. Systemic effects and oropharyngeal complications caused by budesonide were found to be dose-dependent. Candidiasis has been reported by some patients and may occur at therapeutic doses. In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently. (See DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Adults and Children over 12 Years of Age. When treatment with inhaled glucocorticosteroids is started, during periods of severe asthma, and while reducing or discontinuing oral glucocorticosteroids the dosage should be 400-2400 µg daily divided into 2-4 administrations. The maintenance dose is usually 200 - 400 µg twice daily but higher doses may be necessary for longer or shorter periods of time in some patients. The dose of PULMICORT (budesonide) should be individualized to the patient's need and should be the lowest possible dose that fills the therapeutic objective. Once daily dosing may be considered in patients who require a dosage of 400 µg budesonide per day. The dose may then be given in the morning or in the evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually.

Children 6-12 Years. When starting therapy with budesonide in children, during periods of severe asthma and while reducing or discontinuing oral corticosteroids, the dosage should be 200-400 µg daily, given in divided doses twice daily at 100 to 200 micrograms per inhalation. The maintenance dose is individual and should be the lowest dose which keeps the patient symptom-free. Administration twice daily is usually adequate in stable asthmatics.

Children Under 6 Years of Age. Not recommended in children in this age group.

TURBUHALER®: TURBUHALER is a breath-activated dry powder inhaler which does *not* require a coordinated inhalation technique. It contains only the active ingredient budesonide - no propellants or preservatives, and as such, offers those patients sensitive to excipients, an alternate dosage form. NOTE: The patient may not taste or feel any medication when inhaling from the TURBUHALER. This lack of feeling does not mean that the patient is not receiving benefit from PULMICORT TURBUHALER. NOTE: The medication from PULMICORT TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. When prescribing PULMICORT TURBUHALER to young children it is necessary to ascertain that they can follow the instructions for use. The patient may not taste or feel any medication when using PULMICORT TURBUHALER due to the small amount of drug dispensed. Patients should be instructed to rinse their mouths out with water after each inhalation. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.

AVAILABILITY OF DOSAGE FORMS: PULMICORT TURBUHALER is a dry powder inhaler containing 200 doses of 100 µg, 200 µg, and 400 µg or 100 doses of 200 µg of micronized budesonide. Each inhalation from PULMICORT TURBUHALER will provide either 100 µg, 200 µg or 400 µg of budesonide active substance; no additives or carrier substances are included. PULMICORT TURBUHALER cannot be re-filled and should be discarded when empty.

Product monograph available on request.

REFERENCES:

1. Thorsson L. et al. *Eur Respir J* 1994;7:1839-44. **2.** Data on file, Astra Draco study code 36-3027, 1994. **3.** Ernst P, FitzGerald JM, Spier S. *Canadian Respiratory Journal* 1996;3(2):89-100.

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