ORIGINAL ARTICLE

Effect of once-daily generic ciclesonide on exhaled nitric oxide in atopic children with persistent asthma

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KEYWORDS
Airway inflammation; Asthma control; Disease management; Inhaled corticosteroids; FENO; Paediatrics

Abstract

\textbf{Background}: Ciclesonide (CIC) is an effective inhaled corticosteroid for treating asthmatic children. However, its effect on airway inflammation assessed by the fraction of exhaled nitric oxide (FENO) in children with persistent asthma is virtually unknown. We aimed to assess the effect of once-daily generic CIC, 80 or 160 $\mu$g, on FENO, lung function, asthma control and bronchial hyperresponsiveness, in atopic children with persistent asthma.

\textbf{Methods}: This was a 12-week, randomised, double-blind, parallel-group study. Sixty children with mild-to-moderate persistent asthma were recruited. Changes in FENO, asthma control score, lung function (FEV\textsubscript{1}) and bronchial hyperresponsiveness to methacholine (BHR) were used to assess the effects of both CIC doses. Non-normally distributed variables were log-transformed to approximate normality, and parametric tests were used for comparisons within and between groups at baseline and after 12 weeks of treatment.

\textbf{Results}: In the CIC 80 $\mu$g group, FENO decreased from 45.0 ppb (95% CI 37.8–53.7) to 32.7 ppb (95% CI 21.0–47.3) at the end of study ($P=0.021$), whereas in the CIC 160 $\mu$g group, FENO decreased from 47.3 ppb (95% CI 40.4–55.3) to 30.5 ppb (95% CI 24.1–38.7) ($P<0.001$). The difference between groups in FENO at the end of study was not significant ($P=0.693$). There was a significant improvement of asthma control with both CIC doses but there was no significant change in BHR or FEV\textsubscript{1} in either group.

\textbf{Conclusion}: Once-daily generic ciclesonide (80 $\mu$g or 160 $\mu$g), for 12 weeks, is effective to improve airway inflammation and asthma control in atopic children with persistent asthma.

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Introduction

Inhaled corticosteroids (ICSs) are widely recommended as the first-line anti-inflammatory medications for paediatric and adult patients with persistent asthma. Although the effect of different ICSs on asthmatic airway inflammation has been demonstrated in adults, there is much less information regarding childhood asthma, most likely because the invasive methods used in adults to assess the effect of ICSs on airway inflammation are restricted for ethical reasons in children.

FENO is a non-invasive marker of airway inflammation, and it provides useful complementary information for the diagnosis and monitoring of asthma in children.1–3 Together with other lung function tests, FENO has been employed to evaluate the effects of conventional ICSs such as beclomethasone, budesonide and fluticasone,4–6 and also of extra-fine corticosteroid aerosols (mass median aerodynamic diameter of \( \leq 1.2 \mu m \)) such as HFA-beclomethasone and ciclesonide.7,8

Ciclesonide (CIC) is safe and effective for improving asthma symptoms, lung function and BHR in asthmatic children, with apparently undetectable systemic effects.9–14 Although conventional ICSs are effective at reducing airway inflammation as assessed by FENO in asthmatic children,7–9 there is little information about the effect of CIC on airway inflammation in paediatric patients. The available evidence comes from studies mainly involving adults.8,15

The present study was undertaken to determine the effect of once-daily generic ciclesonide, 80 \( \mu g \) or 160 \( \mu g \), for 12 weeks on the level of FENO, asthma control, lung function and airway responsiveness to methacholine in atopic children with mild-moderate persistent asthma.

Methods

This was a randomised, double-blind, and parallel-group study carried out during the year 2013 at the Hospital El Pino, Santiago, Chile. Sixty children (aged 7–15 years) with mild-to-moderate persistent asthma, positive prick test to one or more common aeroallergens, FENO > 25 parts per billion (ppb) and regular treatment with budesonide or fluticasone during the previous 3 months participated in this study. After a 1-week run-in period when children received the ICS as prescribed at their primary care health centres, they were randomly allocated to receive generic CIC (Disbronce, Neumobiotics, CIPLA) one puff of 80 or 160 \( \mu g \) once daily for 12 weeks, with salbutamol as rescue medication. All aerosols were inhaled using a plastic spacer treated with detergent. The devices containing CIC 80 or 160 \( \mu g \) per actuation were indistinguishable from each other and were numbered according to randomisation; patients, parents and study personnel were blinded until finishing the study.

FENO measurements and asthma control assessments were performed every 30 days. Spirometry and methacholine bronchial challenge were performed at baseline and after 12 weeks of treatment. Tests were carried out on two consecutive days in the same order (first FENO, then spirometry and methacholine); salbutamol was discontinued for 12 h before testing, and ICSs were maintained according to prescription. Participating children were not using long-acting beta-2 agonists, oral corticosteroids, anti-histamines, antileukotrienes or theophylline. The primary variable was the change in mean FENO from baseline to the end of the study. Secondary variables were changes in the Asthma Control Test (ACT) score, FEV\(_1\) and BHR to methacholine after 12 weeks of treatment.

On-line single breath FENO measurements (NIOX MINO, Aerocrine AB, Solna, Sweden) were performed according to the ATS guidelines for FENO interpretation.1 Children were asked to inhale to total lung capacity through the mouth-piece connected to the FENO device and then to exhale for 10 s at 50 mL/s, assisted by visual and auditory cues provided by the device.

Spirometry was performed using a pre-Vent flow sensor with the Medgraphics CPFS/D processing system (Medical Graphics Corp.; St. Paul, MN, USA). The percentage of predicted value for each parameter was calculated according to Knudson’s equations.16 Methacholine bronchial challenge was performed if the FEV\(_1\) was \( \geq 80\% \) of the predicted value using a modified Cockcroft’s method.17

A skin prick test for eight common inhalant allergens was performed on the forearm, as was a positive (histamine) and a negative (solvent) control. The following allergens were employed: Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat, dog, Alternaria, a grass mixture, a tree mixture and a weed mixture (Nelco Laboratories, NY, USA). Atopy was defined as a positive reaction (wheat size measuring 3 mm or more after subtraction of the control value) to one or more allergens.

Asthma control was evaluated using the ACT.18 The questionnaires for children aged <12 and \( \geq 12 \) years were filled in by their parents or the children themselves, respectively, during the medical interview, at baseline and every 30 days until the end of study. Physicians were allowed to clarify parents’ and children’s doubts as to the meaning of questions. Patients with a score \( \leq 19 \) were considered to have uncontrolled asthma.

The systemic effect of both CIC doses was assessed by measuring cortisol in 24-h urine samples at randomisation and the end of the study; urinary free cortisol was determined by radioimmunoassay with a reference range of 5–50 \( \mu g/24 \) h. Fungal culture of the oro-pharynx was performed in all patients at baseline and at the end of the study for eventual candidiasis induced by inhaled CIC. Height was measured by stadiometry.

This study was approved by the Scientific Ethics Committee, Chilean Ministry of Health, Southern Metropolitan Area of Santiago, Chile. Full informed and signed consent was obtained from all parents.

Statistical analysis

FENO and all positively skewed variables were log-transformed to approximate normality. Parametric tests (independent and paired samples) were used for comparisons between and within groups, at baseline and at the end of the study; the results of log-converted variables are presented as back-transformed values (i.e., geometric means and 95% CIs). Data were analysed using statistical software (SPSS 15.0, Chicago, USA, and MedCalc 13.2, Ostend, Belgium) and \( P < 0.05 \) was considered statistically
significant. Repeated-measures ANOVA was employed to compare between-group measurements of FENO and ACT that were assessed every 30 days; associations between FENO, PC_{20}, lung function, and ACT at entry were assessed by linear regression. A difference of ≥1 doubling dilution (DD) between baseline and the end of the study was considered a significant reduction of BHR to methacholine. The DD difference was calculated as the log_{10}PC_{20} difference between entry and the end of the study divided by log_{10} 2. A reduction of at least 20% in FENO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb\(^1\) was considered an estimate of a significant response to CIC. The proportion of children in each group (CIC 80 \(\mu\)g and 160 \(\mu\)g) who had a significant improvement in FENO, ACT score and BHR to methacholine after 12 weeks of treatment were compared using the chi-squared test with Yates’s correction for continuity (two-tailed). A power calculation determined 29 patients completing would ensure 85% power (two-tailed, \(\alpha\) error = 0.05) to detect a mean difference of 12 ppb in FENO between treatments (SD = 15 ppb).

Results

Baseline

Of the 60 children who entered the study, 56 completed all visits and measurements: 27 (15 boys) in the CIC 80 \(\mu\)g group and 29 (17 boys) in the CIC 160 \(\mu\)g group (Table 1). Four children were withdrawn from the study: two because of asthma exacerbation requiring oral corticosteroids (one in each group) and two in the CIC 80 \(\mu\)g group because they or their parents were unwilling to continue with study visits and procedures. There was no significant difference between groups (CIC 80 and 160 \(\mu\)g) at baseline or at the end of the study regarding age, height, weight, FENO, methacholine PC_{20}, ACT score, FEV\(_1\), or 24-h urinary free cortisol (Table 1). At baseline, FENO was inversely and significantly related with PC_{20} methacholine (\(P<0.001\), (Fig. 1) and VEF\(_1\)/FVC (\(P=0.036\)), whereas PC_{20} was directly correlated with VEF\(_1\)/FVC (\(P=0.020\)).

![Figure 1](image) Baseline association between FENO and methacholine PC_{20} (regression line, 95% CI and 95% prediction curve).

![Figure 2](image) Mean FENO values (95% CI) at baseline, week 4, week 8 and week 12 in asthmatic children treated with once-daily CIC (80 or 160 \(\mu\)g).

Feno

There was a significant decrease in the geometric-mean FENO level in both groups between baseline and endpoint. FENO in the group treated with CIC 80 \(\mu\)g decreased from 45.0 to 32.7 ppb at the end of the study (\(P=0.021\)), whereas in the CIC 160 \(\mu\)g group, FENO decreased from 47.3 to 30.5 ppb (\(P<0.001\)); see Table 1 for 95% CIs. Both CIC groups showed a significant FENO decrease after four weeks of treatment without further significant changes in measurements at weeks 8 and 12 of treatment (Fig. 2). There was no significant difference between groups in the proportion of children who showed a significant decrease in FENO after 12 weeks of treatment (\(P=0.633\)) and the corresponding percentage for CIC80 \(\mu\)g and CIC160 \(\mu\)g was 59.3 and 69.0%, respectively.

Asthma control

Both doses of CIC significantly improved the level of asthma control after 12 weeks of treatment. The ACT score increased from 19.2 to 23.1 in the group treated with CIC 80 \(\mu\)g (\(P \leq 0.001\)) and from 18.5 to 22.4 in the CIC 160 \(\mu\)g group (\(P=0.003\)). There was no significant difference in ACT between groups at baseline or after 12 weeks of treatment (Table 1). The increase in the ACT score was significant at week 8, with no further significant changes until the end of the study in both treatment groups (Fig. 3). The difference in the proportion of children who had controlled asthma (ACT score 20 or more) at baseline between the CIC 80 \(\mu\)g group (48.1%) and the CIC 160 \(\mu\)g group (41.4%) was not significant.
(P = 0.814). After 12 weeks, 85.2 and 86.2%, in the groups treated with CIC 80 or 160 µg groups, respectively, had controlled asthma, and the difference between groups was not significant (P = 0.783).

Lung function and BHR

There were no significant differences between groups in terms of FVC, FEV1, FEF25–75% or FEF25–75%/FVC at baseline or the end of the study (Table 1), and no significant change in FEV1, FEF25–75% or FEF25–75%/FVC was found within either group after 12 weeks of treatment. However, FVC showed a significant decrease only in the CIC 80 µg group (P = 0.012), (Table 1). The effect of both CIC doses on methacholine PC20 was widely variable, with a mean DD change of 0.72 and 0.55 in the CIC 80 µg and 160 µg groups, respectively (Fig. 4); the two groups had similar magnitudes of DD change (P = 0.731). The difference in the proportion of children who had a DD change ≥1 between the 80 µg (50.0%) and 160 µg groups (32.1%) was not significant (P = 0.304). The geometric-mean PC20 for the CIC 80 µg group was 0.28 mg/mL at baseline versus 0.46 mg/mL at the end of the study but the difference did not reach statistical significance (P = 0.056); in the group treated with CIC 160 µg the difference in PC20 after 3 months of treatment (0.23 mg/mL vs. 0.34 mg/mL) was not significant (P = 0.125).

There was no significant difference in 24-h urinary free cortisol between groups at baseline (P = 0.633) or after 12 weeks (P = 0.537), and there was no significant change within either group after 12 weeks of treatment. Weight and height showed a significant increase in both CIC groups (Table 1), and the difference between groups at the end of the study was not significant: weight (P = 0.993), height (P = 0.728). The mean adherence to treatment with both CIC doses was ≥80%, with no significant difference between groups (P = 0.238), (Table 1). Once-daily CIC at the employed doses was well tolerated, and none of the patients or their parents reported trouble related to the inhaled medication. At the end of the study, none of the patients had positive oropharyngeal cultures for candidiasis.

Discussion

This study shows that once-daily generic CIC either in a dose of 80 µg or 160 µg for 12 weeks is effective at decreasing airway inflammation and improving asthma control in atopic...
asthmatic adults and adolescents aged >12 years has been documented and occurs as early as one week after starting treatment.\textsuperscript{21-25}

The present study did not find a dose-dependent effect of CIC 80 µg or 160 µg on FENO, ACT, lung function or BHR to methacholine. Other authors using original CIC in children with persistent asthma have found a significant dose-response effect between 80 µg and 160 µg for exacerbations and lung function, but not on other outcomes such as BHR to methacholine.\textsuperscript{12-14} An explanation for this lack of a consistent dose-response effect with CIC may be that ICS dose-response curves tend to be flat, with minor differences in clinical and functional results between low and high doses, as shown by evidence-based analysis.\textsuperscript{26} In our study, less than half the patients in both CIC groups improved BHR (DD change ≥ 1) after 12 weeks of treatment. Another study\textsuperscript{14} using original CIC with doses and time spans similar to our study found a significant improvement of BHR to methacholine. However, other authors found that a significant BHR improvement in asthmatic children treated with budesonide was achieved after 4 months of treatment.\textsuperscript{27} Thus, the time to reach a significant effect on decreasing BHR varies depending on factors related to treatment, patients, or disease characteristics, among others.\textsuperscript{28-32} We have previously found a high proportion of BHR to methacholine in children with current asthma symptoms and also in non-asthmatics, which was unrelated to atopy or lung function,\textsuperscript{17} suggesting that environmental factors could increase airway responsiveness not only in asymptomatic asthmatics but also in healthy individuals. Additionally, the lack of a rapid and significant improvement in PC\textsubscript{20} after 12 weeks, as occurred in this study, might also be related to potential pharmacological differences between generic and original CIC, but this remains to be demonstrated by further research.

In the present study, FENO showed a strong association with methacholine PC\textsubscript{20} at baseline but not with ACT or FEV\textsubscript{1}. This finding agrees with other studies showing poor agreement among FENO, symptoms and lung-function measures in asthmatic adults and children.\textsuperscript{21,32} Concordantly, FENO and BHR are more directly related to inflammatory changes in the bronchial mucosa of asthmatic patients than to symptoms or lung function.\textsuperscript{33,34}

CIC is effective at improving asthma control in asthmatic children.\textsuperscript{32,35} The present study, using the ACT questionnaires, found that both CIC doses (80 and 160 µg) produced a similar and significant improvement in asthma control after 12 weeks of treatment. Despite potential limitations of the questionnaires for assessing asthma control in asthmatic children,\textsuperscript{36} the use of validated questionnaires for this purpose is strongly recommended by all major asthma guidelines. In addition, ACT is a better instrument to identify uncontrolled asthma in children than lung function,\textsuperscript{37} with the advantage of being an easily accessible and applicable clinical instrument.

Adherence to treatment is recognised as a crucial element of asthma management and evaluation of treatment efficacy. In asthmatic children, low adherence to ICS treatment results in poor asthma control.\textsuperscript{38} In this study, the adherence to CIC was good (>80%) in both treatment groups. It is likely that regular assessment of adherence to treatment and the education provided to children and parents on the

children with mild-moderate persistent asthma. To our knowledge, this is the first study assessing the short-term effect of a generic CIC on FENO in asthmatic children.

FENO is a recognised marker of airway eosinophilic inflammation and is useful in asthma management for adjusting ICS doses, monitoring the effect of ICSs, verifying adherence to treatment and determining potential responsiveness to ICSs, among others.\textsuperscript{1,19-23} The efficacy of different ICSs, including CIC, in decreasing FENO in
importance of accomplishing the treatments improved the compliance in the present study.

This study has several limitations that are inherent to short-term studies on ICSs. Our study does not allow for predicting long-term adverse events, assessing the variability of therapeutic responses for the different measurements of efficacy, or evaluating the clinical and functional variables determined by seasonal effects (viruses, pollen, indoor and outdoor pollution). Additionally, short-term studies are unable to examine the expected decline of compliance to study medications observed in long-term treatments and the resulting effects on study outcomes. However, the present study, involving a well-characterised group of asthmatic children with mild-moderate persistent asthma, provides evidence on the effectiveness of generic CIC at decreasing inflammation and improving asthma control in those patients. We did not find a significant difference between the effects of CIC 80 and 160 μg on FENO, lung function, asthma control or BHR to methacholine. This could be explained at least in part by the relative flatness of ICS dose-response curves. It might also be related to an insufficient sample size, although other studies that used CIC 80 or 160 μg and which involved several hundred asthmatic children have not found consistent differences in the effects of both doses on study measurements.

It has been shown that CIC is at least as effective as other ICSs for the treatment of asthmatic children, but it does not decrease cortisol excretion. However, the scarcity of data and the important methodological differences among studies make it difficult to draw valid conclusions from comparisons of CIC with other ICSs. Nevertheless, its special pharmacological characteristics (pro-drug, small-particle aerosol, once-daily inhalation, and safety) make CIC an attractive option for the treatment of paediatric asthma; in the case of generic CIC, its lower cost may represent an economic advantage for parents or health institutions.

Conclusions

Generic ciclesonide (80 and 160 μg) inhaled once daily for 12 weeks improved airway inflammation and asthma control in atopic children with persistent asthma.

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Author contributions

All authors participated in the study conception and design; data collection, analysis, and interpretation; manuscript drafting and revision; and approval of the final manuscript.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflicts of interest to declare. The authors alone are responsible for the content and writing of the paper.

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References

9. Skoner DP, Maspero J, Banerji D. Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled...
Dos vacunas en una para un doble beneficio del paciente polisensibilizado
DENOMINACIÓN DEL MEDICAMENTO: Depigoid®DUO. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA: Extractos alérgénicos despigmentados, polimerizados con glutaraldehído y adsorbidos en hidróxido de aluminio, estandarizados biológicamente y cuya concentración se expresa en unidades DPP/ml. Formulaciones:

Composición:

DENOMINACIÓN DEL MEDICAMENTO: Depigoid®DUO. COMPOSICIÓN CuALITATIVA Y CuANTITATIVA:

CONTRAINDICACIONES: b) Efectos adversos graves, neoplasias malignas o enfermedades del sistema inmunológico, por ejemplo enfermedades autoinmunes, por inmunocomplejos o inmunodeficiencias, síntomas graves de alergia, procesos patológicos en los que el paciente recibe betabloqueantes, antidepresivos tricíclicos o inhibidores de la mono-amida-oxidasa, o en los que la adrenalin esté contraindicada, e hipersensibilidad a cualquiera de los excipientes. Advertencias y precauciones especiales de empleo: • Iniciar el tratamiento en periodo asintomático, asegurando que el paciente está clínicamente estable y no existe ninguna situación que contraindique su administración. Comprobar la fecha de administración de la última dosis y la tolerancia a la misma, así como el vial que corresponde administrar, su fecha de caducidad y la dosis. Agitar suavemente el vial antes de extraer la dosis. • Inyectar lentamente por vía subcutánea, en la cara posterolateral del brazo. Se debe evitar estrictamente la administración intravenosa, intracutánea o intramuscular. Alternar los brazos. • Después de la administración del extracto, el paciente debe permanecer en observación, al menos, 30 minutos. No realizar ejercicios o trabajos físicos exhaustivos, ni aplicar baños calientes ni bañarse el día de la inyección. Se aconseja también ese día evitar comidas copiosas y la ingesta de alcohol. No frotar ni aplicar ningún masaje o calor sobre la zona inyectada. Instruir al paciente para que busque asistencia médica en caso de aparición síntomas tardíos de reacción sistémica • Disponer de un equipo de reanimación de emergencia. • En caso de requerirse la administración de dos vacunas Depigoid®DUO de extractos diferentes por separado, se recomienda esperar un intervalo de 2-3 días entre ambas. En caso de no ser posible, se recomienda su inyección en brazos distintos con un intervalo de, al menos, 30 minutos. Interacción con otros medicamentos y otras formas de interacción: No se han realizado estudios de interacción entre Depigoid®DUO y otros medicamentos. No debe mezclarse este preparado con otra vacuna antialérgica, deben administrarse en inyecciones separadas. Los medicamentos que modifiquen la respuesta alérgica (antihistamínicos, corticoides, broncodilatadores, cromonas, antagonistas de los leucotrienos, etc) aumentan el umbral de tolerancia del paciente a la inmunoterapia, si se administran antes de la misma. Pueden surgir reacciones adversas si el paciente olvida tomar su medicación antialérgica habitual antes de la administración de la inmunoterapia. La exposición adicional a alérgenos (exoxena o ialergénica) puede disminuir la tolerancia a la inmunoterapia. No debe administrarse inmunoterapia específica durante el tratamiento con inmunosupresores. La administración de cualquier otro tipo de vacuna (polio, trivalente, etc.) debe realizarse con un intervalo de una semana, anterior o posterior a la administración de este tratamiento. Fertilidad, embarazo y lactancia: No hay datos clínicos sobre un posible efecto de Depigoid®DUO sobre la fertilidad. No hay datos clínicos sobre el uso de Depigoid®DUO en el embarazo ni durante el periodo de lactancia. No se recomienda iniciar tratamiento con Depigoid®DUO en una mujer embarazada. Si se produce el embarazo durante el tratamiento con Depigoid®DUO y la paciente presenta buena tolerancia y respuesta clínica, la inmunoterapia podrá continuarase previa consulta con el médico especialista. Éste realizará una valoración clínica de la paciente para decidir la continuidad o la suspensión de la inmunoterapia. Efectos sobre la capacidad para conducir y utilizar máquinas: En casos muy raros puede aparecer un ligero cansancio. Reacciones adversas: En caso de sobredosis accidental y/o pacientes muy sensibles, pueden presentarse reacciones reactivas adversas locales y/o sistémicas, tanto inmediatas (en los primeros 30 minutos siguientes a la inyección), como tardías (pasados los 30 primeros minutos tras la inyección). Ante la aparición de cualquier reacción adversa se deberá consultar con el médico prescriptor antes de proseguir el tratamiento. Puede ser necesario disminuir la dosis o aumentar los intervalos entre las dosis. Reacción local: Eritema, picor, tumefacción y/o calor en el lugar de la inyección. De manera tardía pueden aparecer nódulos subcutáneos en el lugar de la inyección. Estos nódulos son causados generalmente por el hidróxido de aluminio. Suelen desaparecer con el tiempo, pero pueden persistir semanas o meses. Reacción sistémica: Prurito generalizado, calor generalizado, urticaria, angioedema, tos, rinítis, conjuntivitis, asma leve/moderado, sabor metálico, debilidad, cefalea, disnea, sibilancias, broncoespasmo, estridor, trastornos gastrointestinales con hinchazón, vómitos, dolor abdominal, diarrea, malestar general, mareo, palpitations, sudoración, arritmias, hipotensión, sensación de muerte inminente, sincope, pérdida de control de esfínteres (incontinencia), colapso circulatorio, convulsiones y/o perdida de conciencia. Las reacciones adversas sistémicas pueden poner en peligro la vida del paciente, por lo que ante cualquier indicio de reacción sistémica inmediatamente después de la inyección, aunque sea leve, se debe administrar sin demora tratamiento sintomático antialérgico. En el caso de reacciones sistémicas graves (reacción anafiláctica), es fundamental administrar lo antes posible adrenalin, preferentemente por vía intramuscular, antihistamínicos, oxígeno, broncodilatadores inhalados, corticoesteroides y fluidoterapia. Se aconseja también en estos casos el traslado del paciente a un servicio de urgencias hospitalario para posterior observación. Pauta para la correcta administración de la adrenalin: La adrenalin se administrará preferentemente por vía intramuscular, a una concentración de 1:1.000 y a una dosis de 0,01 ml/kg de peso. Pauta orientativa en caso de ser necesaria una actuación rápida: niños de hasta 6 años: 0,15 ml, niños de 6 a 12 años: 0,3 ml, adultos: 0,5 ml. En caso de persistencia de la reacción sistémica la inmunoterapia deberá repetirse la dosis cada 5-15 minutos, hasta la mejora del paciente. Sobredosis: Un error en la administración del preparado que implique la inyección de una dosis inadecuada y/o la utilización de una vía de administración distinta a la subcutánea, pueden conducir a la aparición de reacciones adversas. PROPiedades FARMACOLÓGICAS: Grupo farmacoterapéutico: Extractos alérgicos. Código ATC V01AA. DATOS FARMACÉUTICOS: Lista de excipientes: Cloruro sódico, fenol, hidróxido de aluminio, agua para inyectables. Incompatibilidades: En ausencia de estudios de compatibilidad, este producto no debe ser mezclado con otros medicamentos. Periodo de validez: Observar la fecha de caducidad que consta en la etiqueta. Precauciones especiales de conservación: Almacenan en nevera (entre 2ºC y 8ºC). No congelar. Naturaleza y contenido del envase: Suspensión en viales de vidrio tipo I, con tapón de bromobutilo (sin látex) y cápsula de aluminio. FECHA DE REVISIÓN DEL TEXTO: Junio 2013.