# Side Effects Similar in Both DMPA Formulations

Major Finding: No significant differences were found in physical or sexual side effects in adolescents taking DMPA-IM and DMPA-SC.

Data Source: Randomized crossover trial of 55

Disclosures: The study was supported by the National Institutes of Health, the Health Resources and Services Administration, and the Indiana Clinical and Translational Sciences Institute. Dr. Williams said she had no conflicts of interest.

## BY ROBERT FINN

From the annual meeting of the NORTH AMERICAN SOCIETY FOR PEDIATRIC AND ADOLESCENT GYNECOLOGY

LAS VEGAS — The intramuscular and subcutaneous formulations of depot medroxyprogesterone acetate seem to have similar side effect profiles in adolescents, according to a randomized crossover study.

Although the side effects of the two formulations (DMPA-IM and DMPA-SC) have been studied in adult women, this is the first study among adolescents, Dr. Rebekah L. Williams said at the meeting.

The randomized crossover study involved 55 young women aged 14-20 years, with a mean of 16.5 years. All participants were either initiating or restarting DMPA therapy. Among the young women, 85% were African American and 20% said they had never had sex.

At baseline, the participants completed surveys about their expectations regarding the side effects, and they were randomized to receive one of the two formulations. At the end of 3 months, participants answered questions about side effects, and then they were given the other formulation. At the end of another 3 months, they were again surveyed, and were permitted to choose which formulation they preferred for a third injection. Thirty-eight of the women completed surveys at all three visits.

The investigators found no significant differences between the two formulations in participants' expectations or experience of physical or sexual side effects. The experience of side effects was not significantly related to expectations of side effects, participants' level of general worry, or their level of general concern about birth control side effects.

With two exceptions, there was no difference in the expectation or experience of side effects between the participants' first and second injections, no matter in which order they received them.

The two exceptions were amenorrhea and irregular bleeding. During the first dose, 10.5% of the participants had amenorrhea, and this increased significantly to 31.6% at the second dose. In contrast, the proportion of women reporting irregular bleeding declined significantly from 26.3% at dose one to 7.9% at dose two.

Dr. Williams of Indiana University, Indianapolis, noticed a mismatch between expectations and experience for sexual side effects. "Over one-third of our sample experienced some change in sexual interest, and one-quarter experienced changes in lubrication during sex," she said. "The striking difference between expectations between physical and sexual side effects may reflect our clinical practice, in that physical side effects are emphasized during contraceptive counseling but sexual side effects may be relatively neglected.

"Clinical counseling should include both physical and sexual side effects, both of which have the potential to significantly impact young women's contraceptive use in the long run."

One difference between the intramuscular and subcutaneous formulations emerged when the women were allowed to choose which one they would receive at the third visit. Of the 38 women who made it to that visit, 26 chose a subcutaneous injection, 9 chose an intramuscular injection, and 3 chose to discontinue DMPA.

"I'm not 100% sure why we [saw] such a striking preference," Dr. Williams said, noting that there were no reported differences in injection pain during the injection, immediately after the injection, or 7 days later.

## **HUMALOG®**

INSULIN LISPRO INJECTION (rDNA ORIGIN)
BRIEF SUMMARY: Consult package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalon or any of its excipients.

Humalog or any of its excipients.

WARNINGS: This human insulin analog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump).

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the "PATIENT INFORMATION" leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in the Humalog physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hyperglycemia or extensis occur during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (see PRECAUTIONS, For Patients Using External Insulin Pumps, and DOSAGE AND ADMINISTRATION).

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (eg, regular, NPH, analog), species, or method of manufacture may result in the need for a change in dosage.

PRECAUTIONS: General—Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (eg, patients who are fasting, have autonomic neuropathy, or are using potassium—lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

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Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment—The requirements for insulin may be reduced in patients with renal impairment.

Hepatic Impairment—Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary.

Allergy—Local Allergy—As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including puritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized malgias have been reported with the use of cresol as an injectable excipient. In Humalog-controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humalog (Inc. 2944) (Pc. 963).

Antibody Production—In large clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-retartment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage of Humalog in External Insulin Pumps—The infusion set (reservoir syringe, tubing, and catheter), Disetronice P ITRON<sup>8220</sup> or D-TRONIpus<sup>8220</sup> cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump such of the external insulin pumps, the infusion set thould be replaced and a new infusion site should be relaced and an ew infusion site sho

selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, For Patients Using External Insulin Pumps, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and Storage).

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic hemoglobin AIC testing, recognition and management of hypoglycemia and hyperglycemia, and periodic assessment for diabetes complications.

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monitoring, periodic hemoglobin ATC testing, recognition and management of hypoglycemia and hyporglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant. Refer patients to the "PATIENT INFORMATION" leaflet for timing of Humalog dosing (<15 minutes before or immediately after a meal), storing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devizes: Before starting therapy, patients should read the "PATIENT INFORMATION" leaflet that accompanies the drug product and the User Manual that accompanies the delivery device. They should also reread these materials each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps, Patients using an external Infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed<sup>ari</sup> Models 506, 507, and 508 insulin pumps with MiniMed<sup>ari</sup> Models 506, 507, and 508 insulin pumps with Mumalog 3 mL cartridges) using Disetronic Rapid<sup>®2</sup> infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON<sup>®2,2</sup> or D-TRONplus<sup>®2,3</sup> cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

A Humalog 3 mL cartridge used in the D-TRON<sup>®2,3</sup> or D-TRONplus<sup>®2,3</sup> or mm should be discarded after 7 days.

and Humalog in the external Insulin pump. Source severy 48 hours or less. Humalog in the external pump should not be exposed to temperature 37°C (98.6°F).

A Humalog 3 mL cartridge used in the D-TRON®23 or D-TRONplus®23 pump should be discarded after 7 days, even if it still contains Humalog, Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin ATC is recommended for the monitoring of long-time glycemic control.

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blood glucose tests, errouc measurement of nemoglobin ALD is recommended or the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity, such as corticosteroids, isoniazid, certain lipid-lowering drugs (eg., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy (see CLNICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin I receptor blocking agents, beta-adrienergic blockers, inhibitors of pancreatic function (eg., octreoidde), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur.

The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately." Mixing Humalog with Humulin® N or Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog.

Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with regular human insulin. 

\*\*Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies with Humalog in pregnant women. Because animal reproduction studies are not always predictive of human response, his drug should be used during pregnancy only if clearly needed.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been rely deviated that the summer of the summer of the summer of the summer of the patients is required throughout pregnancy. During the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

\*\*Nursing Mothers—\*\*It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is doen; meal plan, or both.

\*\*Pediatric Use—\*\*In a 9-month, crossover study of prepubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group; regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately pedror meals 8.4%, and Humalog immediately pedror meals 8.4%, and Humal

ADVERSE REACTIONS: Clinical studies comparing Humalog with regular human insulin did not demonstrate a difference in frequency of adverse events between the 2 treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (see PRECAUTIONS).

Skin and Appendages—injection site reaction, ipodystrophy, pruritus, rash.

Other—hypoglycemia (see WARNINGS and PRECAUTIONS).

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurolo impairment may be treated with intramuscular/subcutaneous glucoagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

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DOSAGE AND ADMINISTRATION: Humalog is intended for subcutaneous administration, including use in select external insulin pumps (see DOSAGE AND ADMINISTRATION). External Insulin Pumps). Dosage regimens of Humalog will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestly evariables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to regular human insulin (ie, one unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent premeal hyperglycemia.

When used as a meatime insulin, Humalog should be given within 15 minutes before or immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal. To achieve optimal glucose-control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than regular human insulin is the patients with diabetes. When not mixed in the same syringe with other insulins, the manular of the patients with diabetes. When not mixed in the same syringe with other insulins, the manular patients in the patients with diabetes. When not mixed in the same syringe with other insulins, them as a sites of the substantial rate of the manular patients in the same individual. Patients must be educated to use proper injection and finitions. Also, the duration of action of Hum

To mL vials

3 mL vials

5 x 3 mL prefilled insulin delivery devices (Humalog\* KwikPen\*\*)

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NDC 0002-7510-17 (VL-7533)

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Storage—Unopened Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the szer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F]) 12 vials, cartridges, Pens KwikPens must be used within 28 days or be discarded, even if they still contain Humalog. Protect from

direct heat and light.

\*\*Discovery of the property of the pro

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